NOVEL SYNTHETIC ROUTES TO 14β,17β-PROPANO AND CYCLOPENTA[14,15] 19-NORSTEROIDS

by

PIA G. MOUNTFORD

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SUPERVISOR: PROFESSOR J. R. BULL

ABSTRACT

Novel Synthetic Routes to 14β,17β-Propano and Cyclopenta[14,15] 19-Norsteroids

Pia Gail Mountford, *Chemistry Department, University of Cape Town, Rondebosch 7700,* February 1995

An efficient synthetic strategy for the stereoselective introduction of a 14β-allyl group to estrone 3-methyl ether has been developed. The approach involves regio- and stereoselective Diels-Alder cycloaddition of acrolein to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate. Hydride reduction of the formyl group of the cycloadduct, followed by tosylation of the resultant primary hydroxy group, gave rise to a 17β-alkoxy 16^1-tosylate. Base-mediated Wharton fragmentation of the 1,3-removed diol derivative produced the 14β-allyl Δ^{15}-17-ketone. Chemoselective conjugate reduction of the ring enone gave rise to 14-allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one in 51% overall yield for five steps.

Regioselective oxidation of the 14β-allyl group furnished precursors for intramolecular coupling reactions with the 17-oxo group, providing access to a series of 14β,17β-propanoestradiol and 'estriol' analogues.

Wacker oxidation of the 14-allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one gave rise to both the 14β-acetonyl and 14β-formylethyl derivatives. The acetonyl enone underwent cerium(III)-mediated aldol condensation with the 17-oxo group to yield the 14β,17β-propano Δ^{15}-estradiol analogue. This series of β-face propano bridged estradiols displayed no competitive binding affinity for the estradiol receptor. The enolisable 14β-acetonyl group was also shown to undergo smooth Michael addition to C(15). The product, 3-methoxy-3'*H*,15α*H*-cyclopenta[14,15]-14β-estra-1,3,5(10)-triene-4'(5'*H*),17-dione, was regioselectively deoxygenated and reduced to yield the 3,17-estradiol analogues. The 3,17β-estradiol displayed promising binding affinity for the estradiol receptor site, whereas the 17α-epimer was biologically inactive.

The 14β-formylethyl enone underwent vinylogous reductive cyclisation with C(15), to yield the 3'-hydroxy cyclopenta[14,15] 17-ketone. No regioselective coupling with the 17-oxo group was observed.

Various attempts to homologate ring D of the 14β-allyl 17-ketone or its Δ^{15}-analogue are described, none of which were successful. However, the silyl enol ether derivative of estrone 3-methyl ether underwent facile cyclopropanation of the Δ^{16}-bond. Iron(III) chloride-mediated cleavage of the zero bridge of the resultant bicyclo[3.1.0] hexanoid intermediate gave rise to the D-homo Δ^{16}-17a-ketone. Conversion of the enone into the derived 14,16-dienyl 17a-ketone furnished an intermediate for conjugate addition studies.

To Karen

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SUMMARY

The first objective of the investigation was to develop a synthetic route to 14β,17β-propano analogues of estradiol. The first part of the overall synthetic strategy entailed the stereocontrolled synthesis of 14-allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one. It was envisaged that regioselective functionalisation of the allyl group would provide precursors for intramolecular closure to the target compounds. An efficient cycloaddition-fragmentation method was developed for the synthesis of the allyl ketone. Thus Diels-Alder cycloaddition of acrolein to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate, followed by hydride reduction of the formyl group of the cycloadduct, and tosylation of the primary alcohol, gave rise to a 17β-acetoxy 16^1-tosylate derivative. The 1,3-disposition of functionality was ideal for Wharton fragmentation to 14-allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one. Chemoselective conjugate reduction of the ring enone gave 14-allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one in 51% overall yield for five steps.

Regioselective functionalisation of the 14β-allyl group under Wacker oxidation conditions gave the 14β-acetonyl derivative, which underwent intramolecular aldol condensation with the 17-oxo group. Standard functional group manipulation of the 14β,17β-propano 17^2-ketone provided the parent 14,17β-propano-14β-estra-1,3,5(10)-triene-3,17α-diol. The initial coupling product could be modified to produce a series of functional variants of estradiol for biological evaluation as competitive binders at the estradiol receptor site.

A hydroboration-oxidation sequence performed on the allyl ketone gave the 14β-formylethyl 17-ketone, which was shown to undergo intramolecular reductive cyclisation with the ring ketone. Deprotection at C(3) furnished the 14,17β-propano-14β-estra-1,3,5(10)-triene-3,17α,17^1-triol analogues.

Wacker oxidation of 14-allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one gave rise to both the 14β-acetonyl and 14β-formylethyl derivatives. The regioselectivity of intramolecular closure of these derivatives was explored. The acetonyl enone underwent cerium(III)-mediated aldol condensation with the 17-oxo group to yield, after standard functional group manipulations, 14,17β-propano-14β-estra-1,3,5(10),15-tetraene-3,17α-diol. The enolisable 14β-acetonyl group was also shown to undergo smooth Michael addition of C(14^3) to C(15). The product, 3-methoxy-3'*H*,15α*H*-cyclopenta[14,15]-14β-estra-1,3,5(10)-triene-4'(5'*H*),17-dione, was regioselectively deoxygenated at C(4') and reduced to yield the estradiol analogues.

The 14β-formylethyl enone underwent vinylogous reductive cyclisation with C(15), to yield the 3'-hydroxy cyclopenta[14,15] 17-ketones. No regioselective coupling with the 17-oxo group was observed.

Preliminary studies directed towards the synthesis of 14,17-propano 17a-homo analogues of estradiol are also described. Two approaches to this objective were explored. In the first, attempts to achieve ring expansion of 14-allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one and the Δ^{15} derivative were unsuccessful, but aspects of the unusual chemistry are described. A second approach was adopted in which estrone 3-methyl ether was converted successively into 17a-homoestra-1,3,5(10),16-tetraen-17a-one and 17a-homoestra-1,3,5(10),14,16-pentaen-17a-one. This entailed methylenation of the silyl enol ether derivative of estrone 3-methyl ether, cleavage of the 16-17 bond to form the 17a-homo Δ^{16}-17a-ketone, formation of the trialkylsilyl dienyl ether derivatives, and palladium-mediated dehydrosilylation to give the 14,16-diene 17a-ketone.

Aspects of the regio- and stereoselectivity of conjugate functionalisation of the 14,16-diene 17a-ketone are described, and a preliminary account is given of the feasibility of introducing a 14-allyl group into the 17a-homo dienone.

Several of the compounds synthesised in this investigation were subjected to biological activity studies, and structure-activity trends are discussed.

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Chapter 1

INTRODUCTION

Estrogen plays a vital role in the growth and differentiation of a variety of tissues, as well as acting as regulators of various physiological processes in the body.[1,2] A deficiency of estrogen is detrimental to health, causing postmenopausal symptoms and osteoporosis, among other complaints. However, although estrogen-replacement therapy is a viable option for the symptomatic treatment of many of these ailments, orally-administered estradiol suffers the disadvantage of weak activity and a short active lifetime owing to the harsh metabolic environment encountered by the hormone in the digestive tract.[3] Synthetic estradiols possessing greater activity and more metabolic resilience than the parent hormone have thus long been the subject of numerous investigations. One of the earliest effective synthetic modifications of estradiol involved the introduction of a 17α-ethynyl moiety (Figure 1.1).[4] The resultant tertiary alcohol at C(17) is less susceptible to metabolic degradation. As a consequence, ethynylestradiol is 15-20 times more orally-active than the parent hormone.

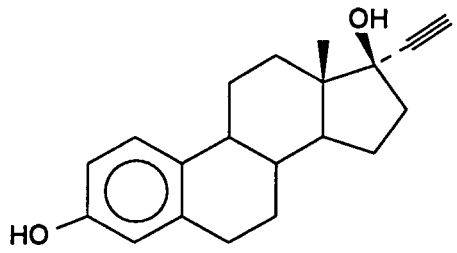


Figure 1.1: Ethynylestradiol

In the 1970's, the C(7) and C(11) positions were identifed as significant in influencing the activity of estradiol. Moxestrol, the 11β-methoxy derivative of ethynylestradiol, is a highly potent estrogen. 11β-Ethoxy substitution also tends to increase the stability of the estrone receptor complex. The 11α-methoxy isomer, however, is a partial agonist/antagonist, binding weakly and reversibly with the receptor, and is comparable to estriol in terms of biological activity.[5] The introduction of bulkier substituents at C(11) eg. allyl, vinyl, propyl, and substituted phenyl groups also appears to enhance the relative binding affinities of these synthetic hormones. This approach of varying the steric environment in a position where receptor affinity can be increased is

standard practice in terms of defining boundary conditions for receptor site access. A 7α-methyl substituent increases the affinity of the molecule for the estradiol receptor site, whereas the combined effect of a 7α-methyl and 11β-methoxy substituent results in almost a total loss of affinity for the receptor.[5] It is proposed that the two substituents projecting above and below the plane of the steroid skeleton block access to the receptor recognition site. This and other findings that minor chemical alterations of the natural hormone could alter the stability of the receptor-hormone complex sparked off a broad investigation into structure-activity relationships in steroidal hormones.

Rational drug design is based on an understanding of the three-dimensional structure of the active sites of proteins, thereby allowing the chemist to create ligands with the appropriate fit and reactivity to induce or block certain biological responses. This approach is not feasible in the steroid field since pure, stable steroid receptor proteins have not yet been isolated and crystallised for X-ray analysis.[6] Consequently, an understanding of the molecular basis of steroid-protein interactions has evolved through the use of two approaches: a) molecular modelling to predict and/or approximate the steroid hormone receptor binding site, and b) collection of biological binding and activity data for large numbers of synthetic ligands in order to relate structure to activity on an empirical basis, and to map out an imprint of the active site.[6] These two philosophies are approaching convergence owing to the collection of crystallographic data on over 1000 steroid hormone analogues, which allows for a comparison of patterns of conformational preference and intermolecular interactions observed in single crystal studies with data on the binding affinities of the same steroids for protein targets.[7] Ultimately, the accumulation of a sufficiently comprehensive structure-activity database is hoped to introduce the scope for predictive hormone design.

Two types of groups appear to influence binding to the receptor: the functional groups, in the absence of which no or minimal binding occurs, and the modulating groups which seem to influence the ability of the functional groups to interact with the receptor by creating a favourable or unfavourable environment.[8] However, while receptor binding is essential in order to elicit specific biological responses, it is not sufficient. Antihormones may bind to the receptor, but fail to activate it.[9] The principle structural differences between steroids that bind well to the estrogen receptor as opposed to other hormone receptors is the presence of the phenolic ring A. The hydroxy group at C(3) of the phenol ring of estradiol acts as a hydrogen-bond donor, and this bond is thought to be more important than the conformation of the molecule in terms of estrogen receptor binding.[5,9] This was exemplified by the potent non-steroidal estrogen diethylstilbestrol, which contains two phenolic rings capable of mimicking ring A of estradiol (Figure 1.2).

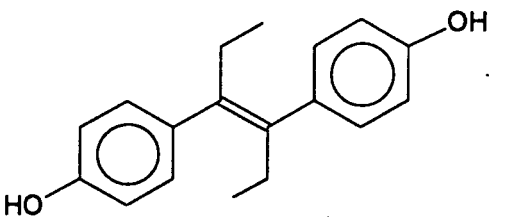
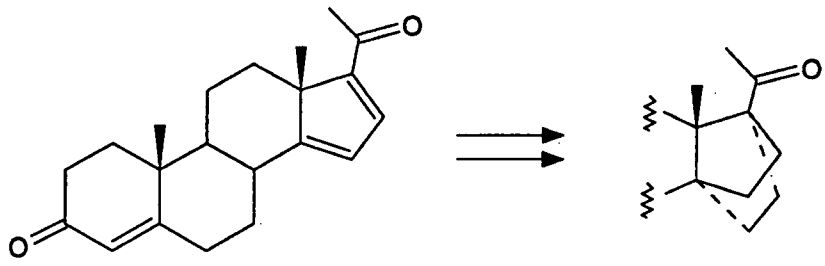


Figure 1.2: Diethylstilbestrol

Blocking of the 3- and/or 17β-hydroxy groups of estradiol by methylation and/or esterification results in a loss of binding affinity, thus establishing the importance of these two polar groups on the otherwise hydrophobic skeleton.[8] Thus, while an examination of the structures of compounds with high affinity for estrone receptors suggests that receptor *binding* is primarily the result of a tight association between the receptor and the steroidal ring A, it is the conformational features of, and the functional groups on the D-ring that control hormone *activity* by inducing or stabilising subsequent receptor functions, and by interacting directly with chromatin in order to modulate gene transcription.[9] Ring D modified steroid hormones have therefore long been the subject of numerous investigations.

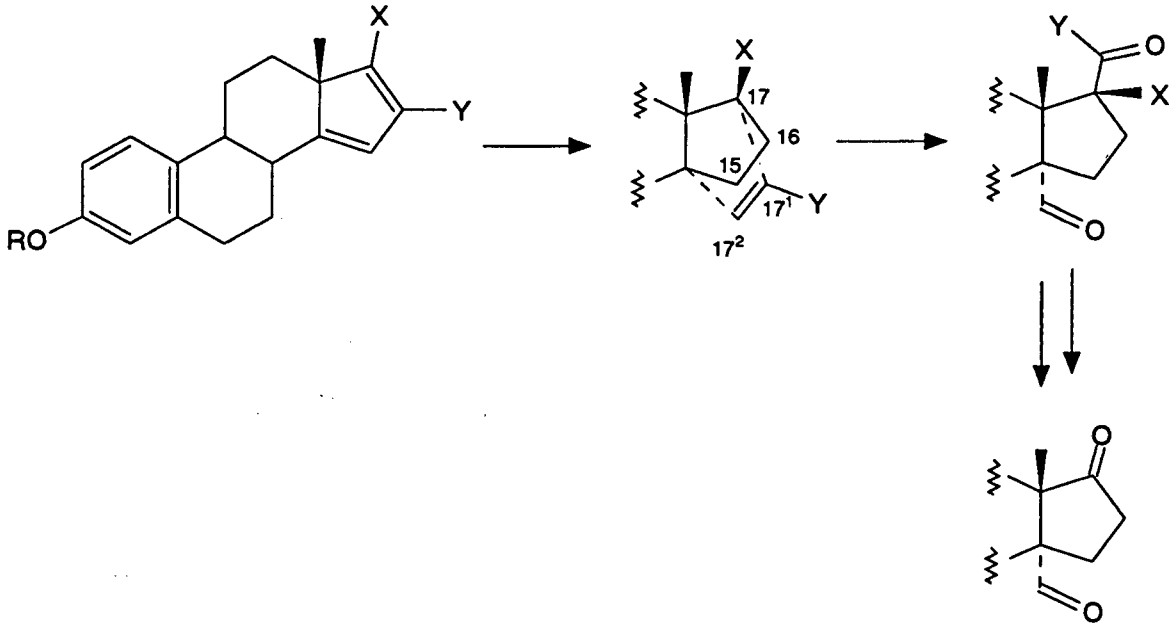
During the 1960's, for example, it was known that hormone analogues with 17α-alkyl groups often displayed enhanced biological activity (*cf.* 17α-ethynylestradiol). In order to monitor the effects of restricting the conformational freedom of the 17α-substituent, Solo *et al.* introduced a two-carbon bridge between the 14α- and 17α-positions of progesterone via cycloaddition of methyl acrylate to a ring D 14,16-diene (Scheme 1.3).[10] The derivative demonstrated antiprogestational activity. This finding was explained by invoking the importance of the 17β-acetyl substituent in progesterone binding. By introducing the etheno bridge, this group was deflected towards the α-face, thereby influencing the activity.[11] Extensive investigations into bridged and bridge-functionalised analogues of natural hormones have been described by Solo.[12]

Scheme 1.3



This cycloaddition approach to the introduction of a 14α,17α-ethano bridge has been adopted by other workers. As part of an investigation into pathways to 14α-alkyl 19-norsteroids, the highly stereoselective Diels-Alder cycloaddition of an ethylene equivalent to a steroidal 14,16-diene was exploited.[13] Oxidative cleavage of the residual olefinic bond provided a route to restoring the ring D system with concomitant introduction of a 14α-formyl group (Scheme 1.4).

Scheme 1.4



Certain of these 14α,17α-ethanoestradiol and estriol analogues displayed enhanced oral estrogenicity on biological evaluation (Figure 1.5).[14]

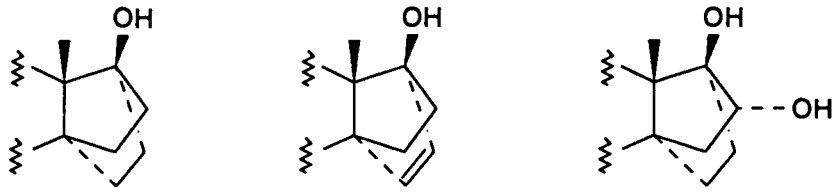
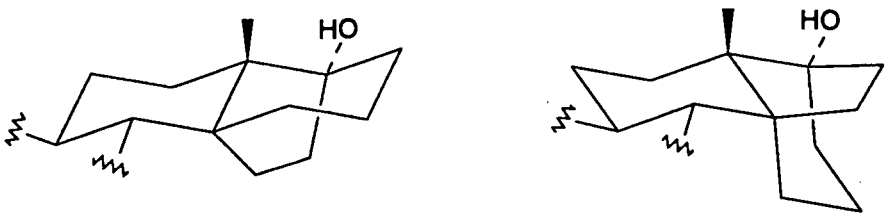


Figure 1.5: Active bridged estradiol and estriol analogues

It is generally accepted that steroid-receptor binding interactions are primarily hydrophobic, except for specific polar interactions.[15] As part of the ongoing investigation into stucture-activity relationships in estrone hormones, this finding that the introduction of a ring D ethano bridge proved beneficial to binding and activity, provided enormous scope for extending the principle of ring D bridging as a structure-activity probe for estradiol and estriol analogues, hopefully providing some insights into the nature of the hormone binding pocket in the process.

As part of a study to determine the boundary conditions for estrogen activity of these bridged systems, this project set out to investigate the influence of increased 14,17-bridge size on biological activity of estradiol analogues. Accordingly, it was necessary to develop stereocontrolled synthetic routes to 14β,17β-propano analogues of estradiol (Figure 1.6). Molecular modelling reveals that these analogues closely resemble the active 14α,17α-ethano compounds, but introduce subtle differences in the spatial orientation of the 17-hydroxy group. A parallel investigation into the synthesis and biological activity of 14α,17α-propano analogues of estradiol has been conducted.[16] These studies are expected to provide clear evidence of structure-activity trends associated with expansion of the 14,17-bridge in this class of hormone.



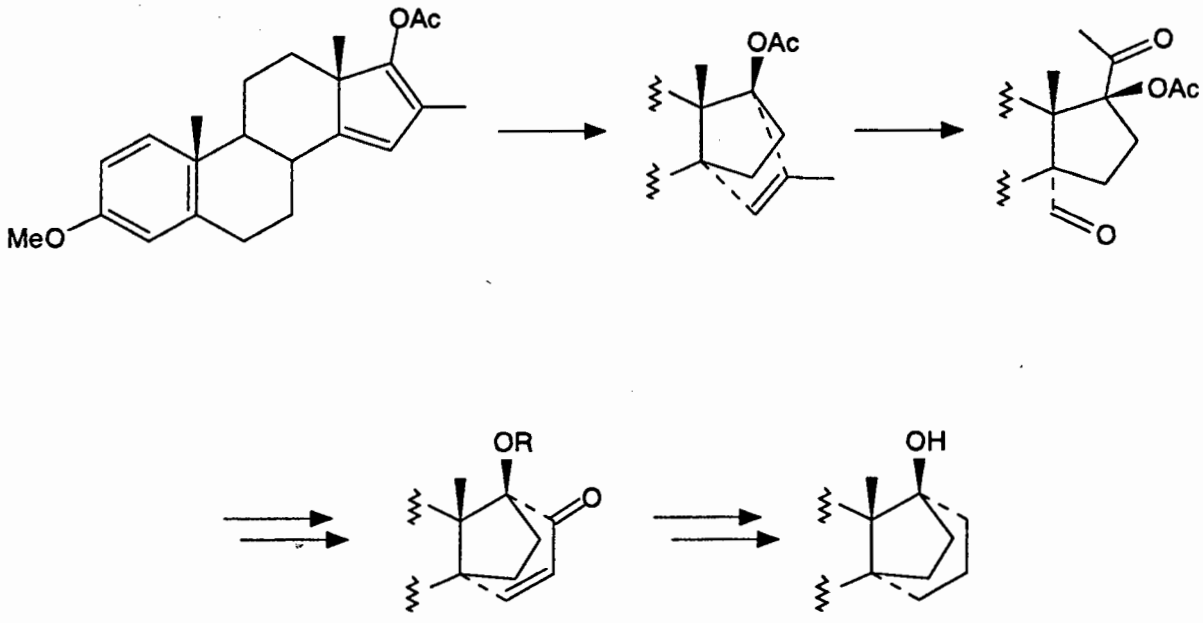
14β,17β- Propanoestradiol

14α,17α- Propanoestradiol

Figure 1.6: Expanded ring D bridged analogues

The strategy for the synthesis of 14α,17α-propanoestradiol entailed a cycloaddition - oxidative cleavage sequence on 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate, followed by aldol condensation of the 17α-acetyl 14α-carbaldehyde (Scheme 1.7).[16]

Scheme 1.7



Retrosynthetic analysis of 14β,17β-propanoestradiol. Estrone 3-methyl ether is an appropriate starting material in this study, since it is readily available, and the essential features pertaining to the 19-norsteroid skeleton are in place. Retrosynthetic analysis based upon disconnections of the propano-bridge bonds in the target molecule leads to four intermediate structures variously alkylated at C(14) and/or C(17) (Figure 1.8).

Synthon **a** requires the introduction of a three-carbon element from the β-face of estrone. This configuration at C(17) would be unfavourable for ready synthetic access, but more importantly, difficulties would be experienced in the closure of the 17β-propyl moiety with C(14).

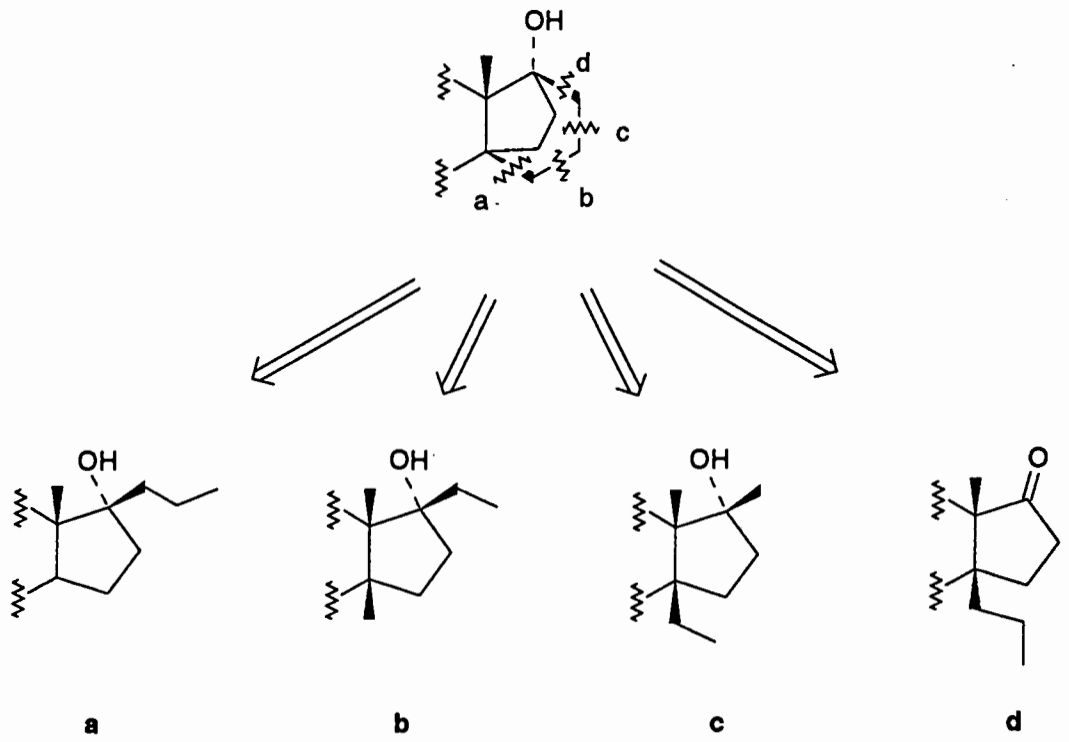
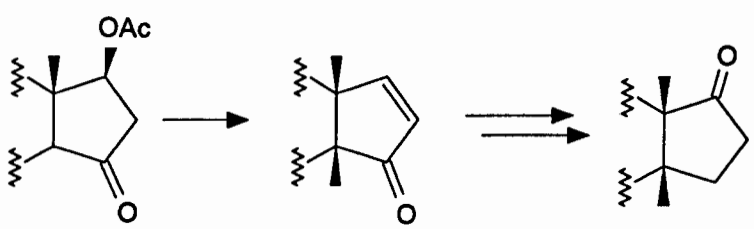


Figure 1.8: Retrosynthetic analysis

Synthon **b** requires the introduction of a functionalised 14β-methyl residue and a 17β-ethyl fragment. 14β-Methyl 19-norsteroids have been synthesised via base-mediated methylation of 15-ketones, followed by functional group transposition from C(15) to C(17) (Scheme 1.9).[17] However, this methodology is unlikely to be applicable to the objective of synthon **b**, since a 14β-functionalised methyl group is a prerequisite for subsequent intramolecular closure.

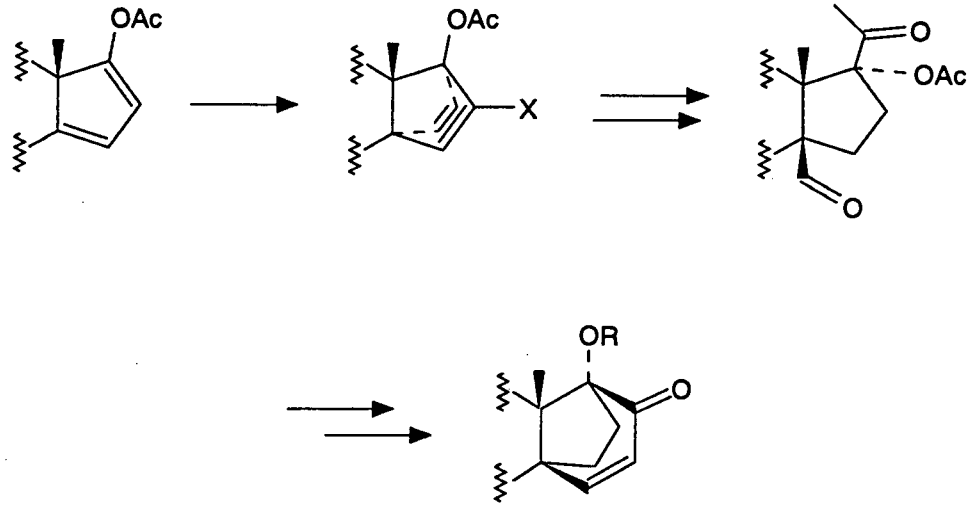
Scheme 1.9



Investigation of synthon **b** as a retrosynthetic precursor to 14β,17β-propanoestradiol, however, is the basis of another study.[18] The synthetic strategy

involved cycloaddition of an propyne equivalent to a ring D diene, followed by chemoselective modification and oxidative cleavage of the β-bridge (Scheme 1.10).

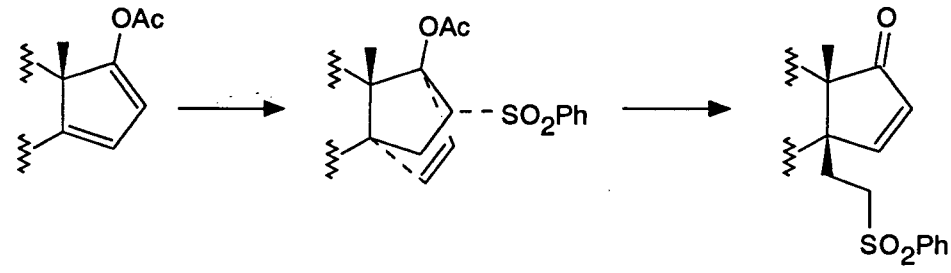
Scheme 1.10



Synthon **c** requires 14β-functionalised ethyl and 17β-functionalised methyl groups as precursors for closure. This approach is conceptually similar to that outlined for synthon **b**.

The final disconnection to synthon **d** appears to offer the most scope for further retrosynthetic analysis, since it entails the stereoselective introduction of a functionalised alkyl group at C(14), for which precedent already exists. This was achieved by a cycloaddition-retrograde cleavage sequence. Cycloaddition of phenyl vinyl sulfone to a 14,16-dienyl acetate, followed by retrograde opening of the cycloadduct in the presence of base, gave the 14β-(2-phenylsulfonylethyl) 17-ketone (Scheme 1.11).[19]

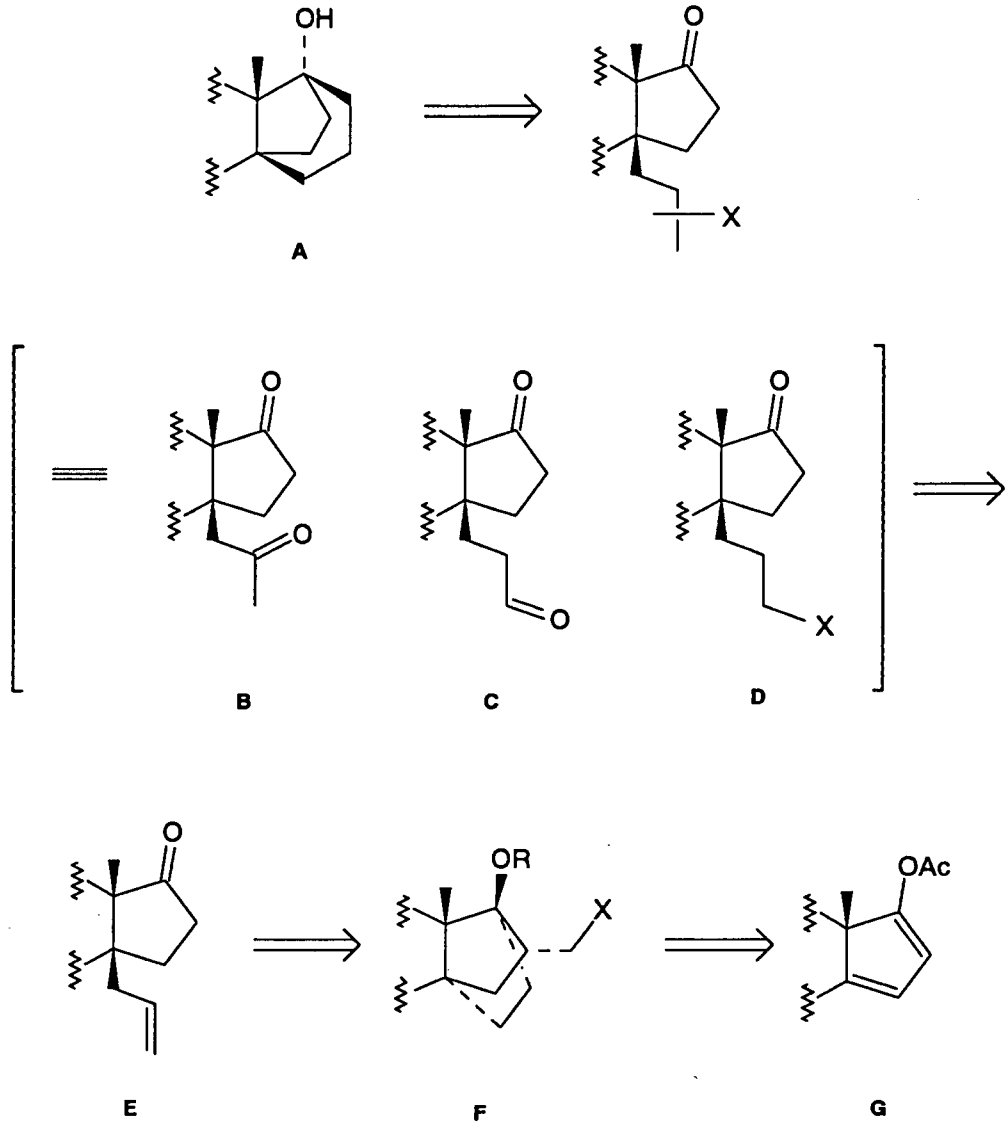
Scheme 1.11



Regioselective functionalisation of the 14β-alkyl moiety would allow for intramolecular coupling of the three-carbon fragment with the 17-carbonyl group. Thus,

the 14β-acetonyl 17-ketone (**B**), the 14β-formylethyl 17-ketone (**C**), and the terminally functionalised (eg. X=halide) 14β-propyl 17-ketone (**D**) were identified as three real intermediates of synthon **d** which would possess suitable functionality for intramolecular closure to the target 14β,17β-propanoestradiol (**A**). It was evident that these intermediates shared a common precursor, the 14β-allyl 17-ketone (**E**). The allyl ketone could, in turn, be obtained from a fragmentation or a retrograde reaction of a suitably-functionalised cycloadduct (**F**). The overall retrosynthetic plan is depicted in Scheme 1.12.

Scheme 1.12



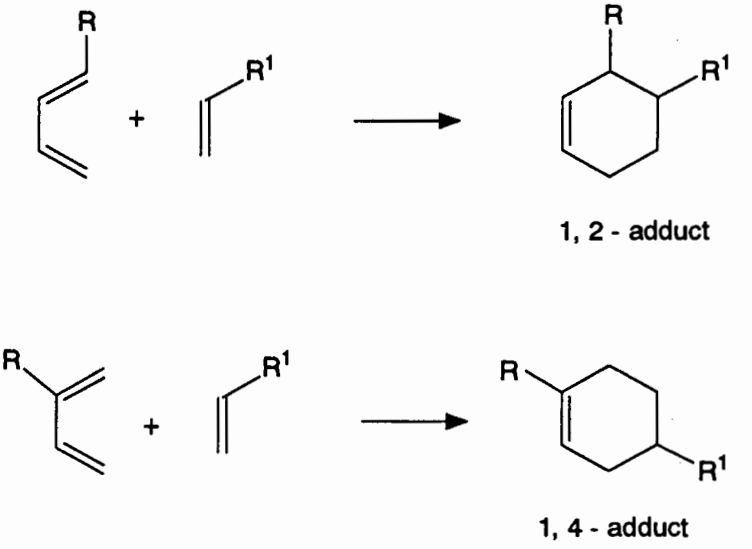
Synthetic Strategies Towards the Synthesis of 14β,17β-Propanoestradiol. Cycloaddition of a three-carbon dienophile possessing suitable functionality to a ring D 14,16-diene, followed by a Grob fragmentation of the 1,3-removed diol derivative, was expected to provide access to the 14β-allyl 17-ketone. The fragmentation would thus provide a route to the stereoselective introduction of a functionalised propyl moiety at C(14), with concomitant restoration of the D-ring and the 17-oxo group.

The diene of choice was the 14,16-dienyl 17-acetate derivative of estrone 3-methyl ether (**G**). The conversion of estrone to the dienyl acetate is well-described in the literature, the three-step α-bromination, dehydrobromination, and enol acetylation sequence proceeding in *ca* 60% overall yield.[20] Ring D conjugated dienes are known to be reactive,[21] and this dienyl acetate derivative had been used successfully in numerous cycloaddition studies. The β-face of the cyclic diene is found to be less hindered than the α-face,[12] and is thus sterically and stereoelectronically more accessible to the dienophile.

The Diels-Alder reaction involved is a $[\pi 4_s + \pi 2_s]$ cycloaddition. This reaction has the advantage of predictability of product regio- and stereochemistry. With cyclic dienes, an unsymmetrical dienophile can add *endo* or *exo*. *Endo* addition tends to predominate under kinetically-controlled conditions due to secondary orbital overlaps of frontier orbitals not directly involved in new bond formation, thus lowering the energy of the transition state with respect to the *exo* transition state where these interactions are absent.[22] The substitution patterns of the components of a Diels-Alder reaction have a strong influence on the regiochemical outcome of the reaction. If the diene is 1-substituted, the diene and dienophile substituents will be predominantly 1,2-disposed ('ortho') in the cycloadduct. For 2-substituted dienes, the 1,4-adduct ('para') predominates (Scheme 1.13). This regioselectivity is determined by the size of the coefficients of the orbitals involved in the overlap. Interactions between two large and two small terminal coefficients are more favourable than between two large-small overlaps.

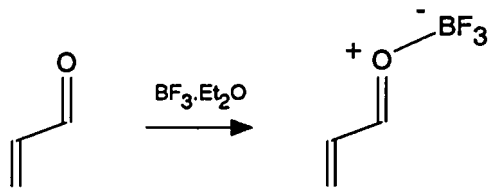
A cycloadduct arising from acrolein as the dienophile would be ideal for the requirements of this study, if the regioselectivity of cycloaddition was good. A normal Diels-Alder cycloaddition is dominated by the $HOMO_{diene}$-$LUMO_{dienophile}$ interaction, this giving rise to the most energetically-favourable frontier molecular orbital overlap.[22] An electron-withdrawing substituent on the dienophile lowers its LUMO energy, resulting in a greater HOMO-LUMO interaction in the transition state ie. the dienophile is activated. Acrolein, with its formyl group substitution of the double bond, is thus an appropriate dienophile.

Scheme 1.13



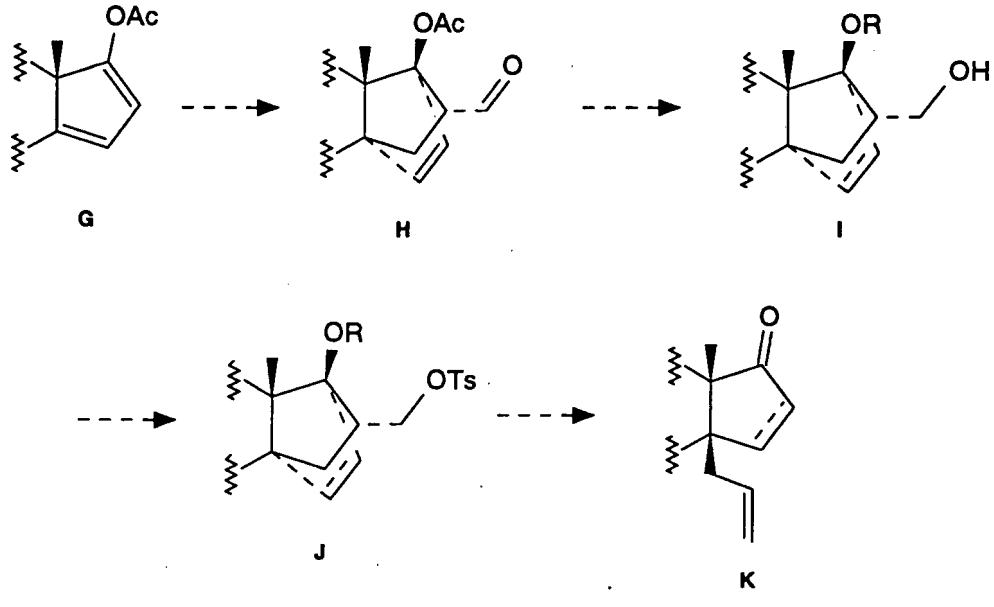
[4 + 2] Cycloadditions are usually thermally-mediated, in accordance with the Woodward and Hoffman rules. The dienyl acetate (**G**), however, while thermally stable under neutral conditions, is sensitive to the presence of acid or base during cycloaddition. Acrolein is a notorious dienophile, polymerising rapidly in the presence of acid, base or heat. Mild reaction conditions and rapid cycloaddition were thus required for this step to be efficient. We expected to improve the reactivity of the acrolein by employing a Lewis acid catalyst, thereby facilitating a milder cycloaddition. Lewis acid catalysed Diels-Alder cycloadditions are not only faster, but are also more stereo- and regioselective than uncatalysed reactions.[23] The Lewis acid (eg. boron trifluoride-diethyl ether complex) complexes with suitable dienophiles, in this case acrolein, thereby enhancing its allyl cation-like nature. In terms of frontier orbitals, this results in a lowering in energy of the LUMO, which gives rise to a greater $HOMO_{diene}$-$LUMO_{dienophile}$ interaction in the transition state, and thus increases the reaction rate. Increased polarisation of the C=C double bond LUMO increases regioselectivity, and the larger LUMO coefficient on the carbonyl carbon results in larger secondary orbital overlap, thus leading to enhanced *endo*-selectivity (Scheme 1.14).

Scheme 1.14



In the light of these theoretical considerations and precedent, it was expected that Diels-Alder cycloaddition of acrolein to the dienyl acetate (**G**) would give rise to a regio- and stereodefined adduct (**H**) (Scheme 1.15). Modification of the residual carbaldehyde group of **H** via reduction to the primary alcohol (**I**), followed by tosylation, would set the 1,3-diol derivative up for Wharton fragmentation. Thus, base treatment of the 17-acetoxy 16^1-tosylate (**J**) would be expected to give rise to the key intermediate 14β-allyl 17-ketones (**K**). This sequence could be performed on the primary cycloadduct (**H**) or on its $17^1,17^2$-dihydro derivative.

Scheme 1.15

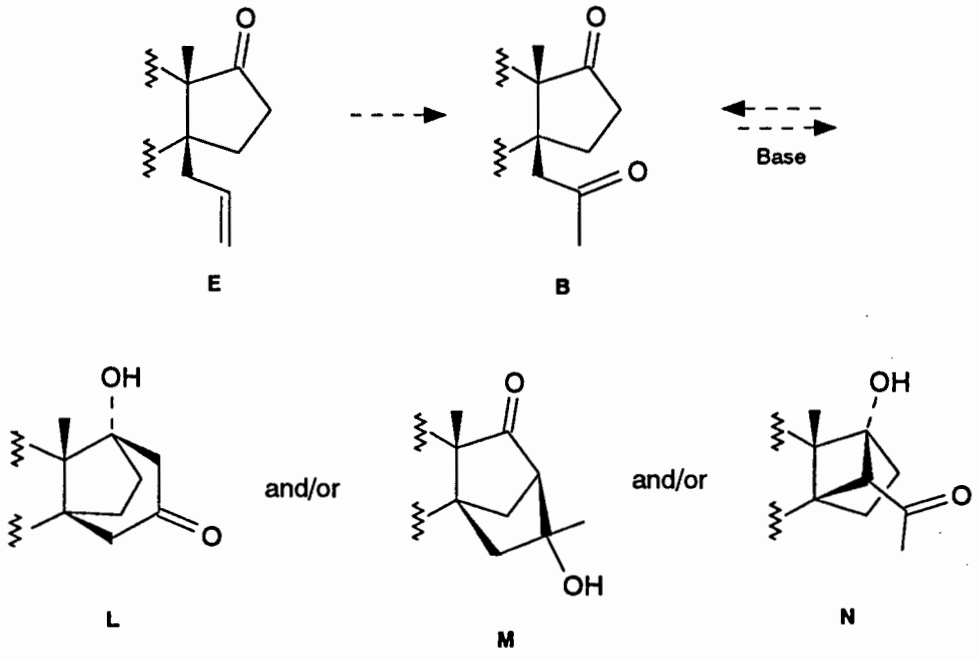


Wharton fragmentations can occur in systems possessing a cyclic 1,3-diol derivative in which there exists an *anti*, but not necessarily antiperiplanar, relationship between the two bonds undergoing cleavage.[24] If the alkoxide produced upon deprotonation of the diol derivative is constrained to exist in an extended conformation, then fragmentation is highly favourable. If, however, the anion is forced to adopt another

conformation, fragmentation may be accompanied by intramolecular displacement, leading to oxetane formation. Models indicated that the 17β-acetoxy 16[1]-tosylate (**J**) is predisposed to fragmentation, but that other side reactions under fragmentation conditions *viz.* intermolecular nucleophilic substitution and elimination of the leaving group could not be ruled out.

Regioselective functionalisation of the 14β-allyl group in compound **E** in order to generate a suitable substrate for intramolecular closure with C(17) was the next consideration. Oxidation of the allyl group to form the derived 14β-acetonyl 17-ketone (**B**) was expected to allow for an transannular aldol condensation, based on classical Robinson annulation methodology, leading to the target 14β,17β-propano seleton.[25] The outcome of this aldol condensation route was, however, uncertain since base treatment of the acetonyl ketone (**B**) could, in principle, give rise to three products of intramolecular enolate addition to a ketone (Scheme 1.16). Furthermore, the desired product (**L**) was expected to be susceptible to retroaldol cleavage, since the aldol condensation is essentially a reversible reaction.

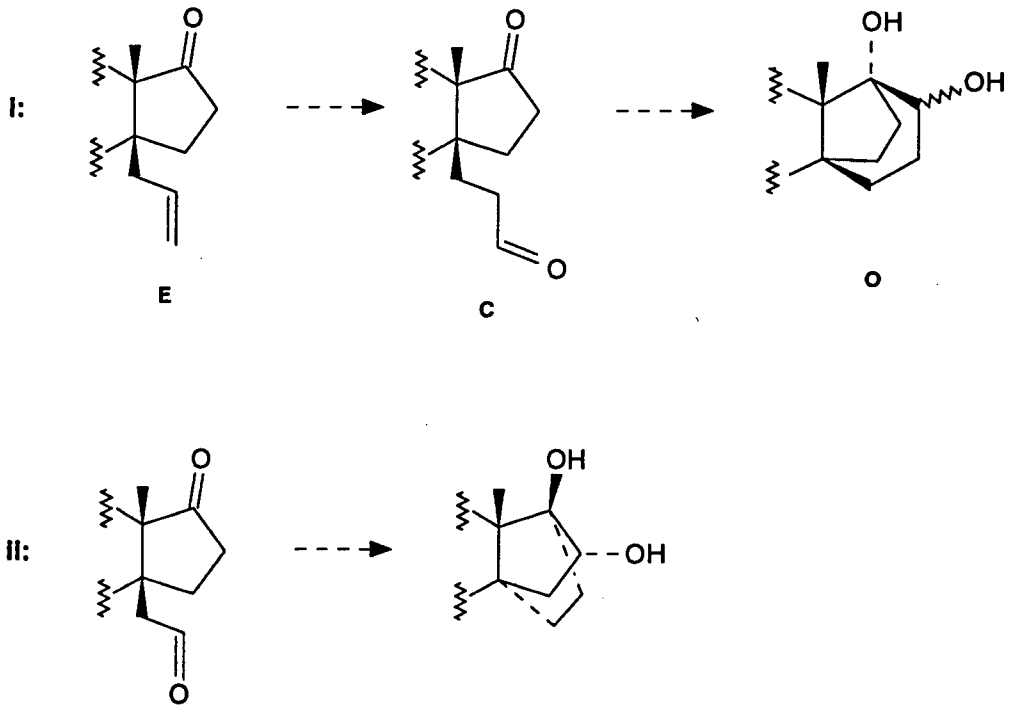
Scheme 1.16



A complementary approach, involving terminal oxidation of the allyl ketone (**E**) leading to a 14β-formylethyl 17-ketone (**C**), was expected to provide an intermediate for intramolecular reductive cyclisation (Scheme 1.17, **i**). Aldehydes and ketones, usually cyclic ketones, can undergo this pinacol-type coupling under the influence of active metals such as magnesium, titanium, zinc, and aluminium.[26] This type of intramolecular

cyclisation was exploited by Neef *et al.*[27] in the synthesis of the epimeric 3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-16β,17ξ-diols (Scheme 1.17, **ii**). This approach was not subject to the uncertainties surrounding the intramolecular aldol closure route. A parallel investigation would thus allow for a comparison of pathways to the 14β,17β-propano compounds.

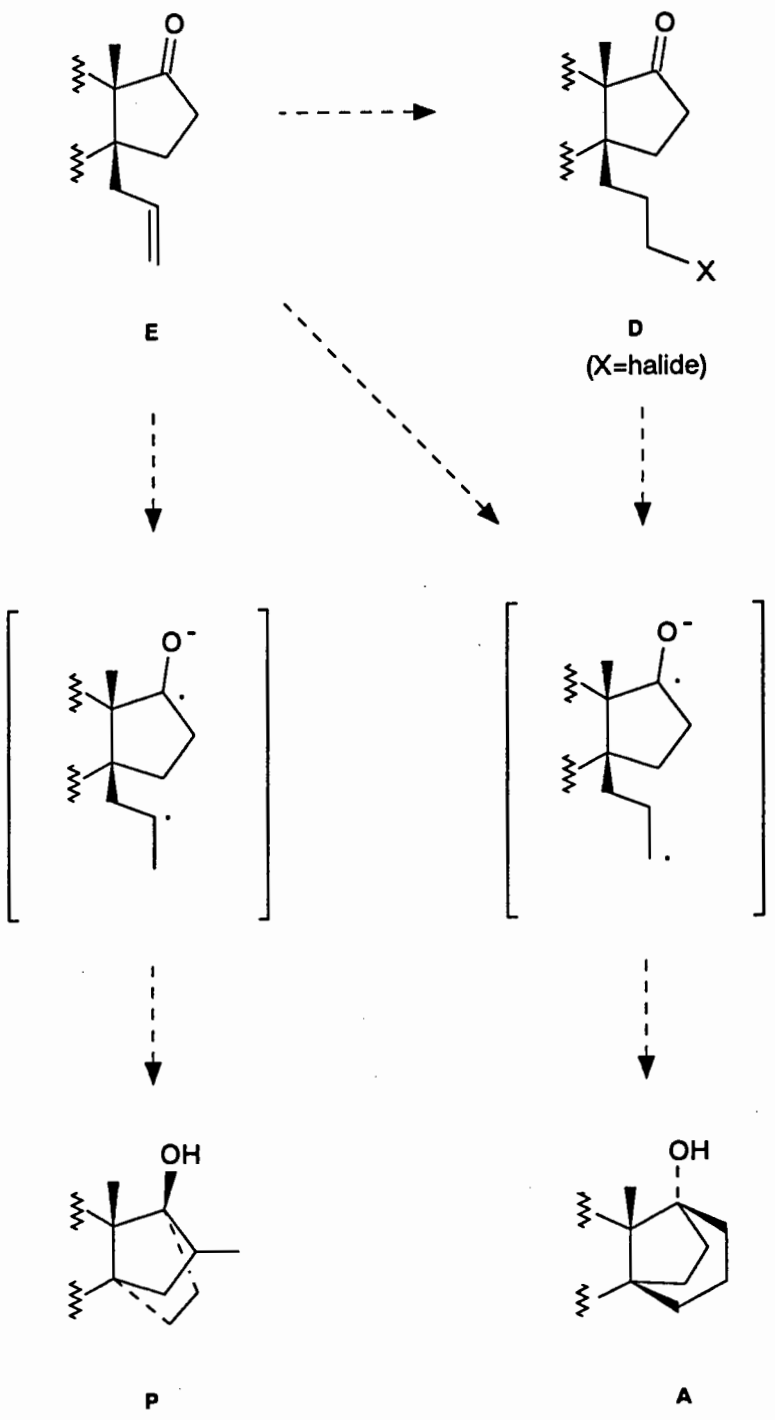
Scheme 1.17



Both closure products (**L** and **O**) would possess functionality on the new propano ring which could be exploited to generate a series of functional variants of the parent 14β,17β-propanoestradiol analogues for biological evaluation as competitive binders at the estradiol receptor site.

Finally, terminal halogenation of the 14β-allyl group of the allyl ketone (**E**) would give rise to an intermediate for radical-mediated cyclisation. Both carbonyl-alkyl halide and alkyl halide-olefin couplings are feasible in terms of radical cyclisation methodology,[28] but the product of the latter (**P**) would be inappropriate for the requirements of this study (Scheme 1.18).

Scheme 1.18

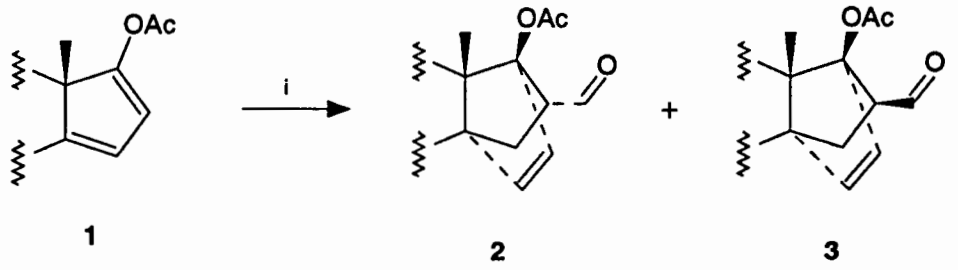


Chapter 2

SYNTHESIS OF 14β-ALLYL-3-METHOXY-14β-ESTRA-1,3,5(10)-TRIEN-17-ONE

The Diels-Alder cycloaddition was performed between 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**) and acrolein at 20°C in the presence of boron trifluoride diethyl ether complex to give mainly the cycloadduct (**2**) (82%) accompanied by a small amount (7%) of a minor isomer (**3**) (Scheme 2.1).

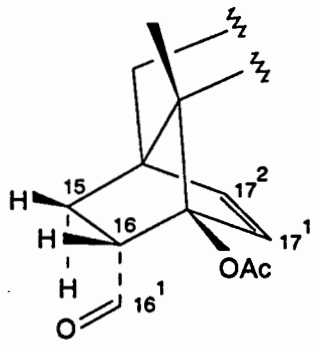
Scheme 2.1



1 **2** **3**

i, Acrolein, BF_3Et_2O

Mass spectral and microanalytical data indicated that a cycloaddition had taken place. The NMR spectrum of **2** provided confirmation of the proposed structure. The signal for 16β-H appeared at δ 3.09 (dt, *J* 8.7 and 2 x 4.4 Hz). This is consistent with the expected structure, with one large *exo-exo* coupling between 16β- and 15β-H and smaller, coincidentally identical couplings of 16β-H with the 15α- and 16^1-protons (Figure 2.2). The large coupling was confirmed by the appearance of the formyl proton signal at δ 9.49 (d, *J* 4.4 Hz). Confirmation of the *endo*-disposition of the carbaldehyde group is discussed later. Furthermore, the 17^1- and 17^2- protons of the etheno bridge resonated as an AB multiplet at δ 6.22 and 6.37 (each d, *J* 6.3 Hz).



2

Figure 2.2: Perspective view of the cycloadduct (**2**)

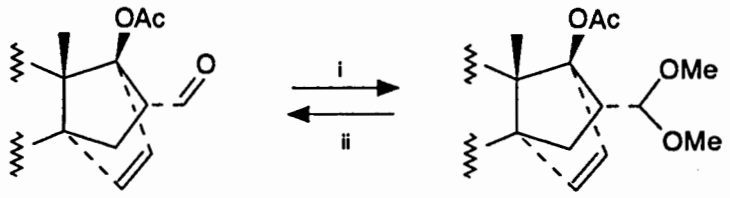
In the NMR spectrum of the minor cycloadduct (**3**), the 16α-proton resonated as a doublet of doublets (*J* 9.4 and 4.5 Hz) at δ 3.11. Although *exo-exo* couplings are usually larger than *endo-endo* couplings for comparable systems, the range of *J* values is relatively wide, and there could be some discrepancies in the relative sizes of couplings. It would seem unlikely, in view of the theoretical expectations and analogy, that this compound is a regioisomer of the major adduct, even though a 15-H_{exo} would account for the large coupling. The 16^1-proton resonated as a singlet, thereby reflecting its orthogonal relationship with 16α-H. Apart from the differences in the 16- and 16^1-signals, the ^{1}H-NMR spectra of **2** and **3** were comparable.

The 16-formyl group of the cycloadduct (**2**) was found to be somewhat reactive. Crystallisation of material recovered directly from the cycloaddition reaction from dichloromethane-methanol gave rise to a more polar compound (TLC) in 20% yield. This was assigned the structure (**4**), arising from acetalisation of the formyl group of the cycloadduct (**2**) by methanol in the presence of traces of Lewis acid. (Scheme 2.3). Analytical data indicated the elements of methanol addition, and the presence of the dimethyl acetal was confirmed by the presence of two three-proton singlets at δ 3.28 and 3.31 in the ^{1}H-NMR spectrum of acetal (**4**). The 16^1-proton displayed the expected upfield shift, resonating as a doublet at δ 4.13 (*J* 8.6 Hz). The 16β-proton signal at δ 2.76 (dt, *J* 2 x 8.6 and 3.9 Hz) reflected this coupling. COSY and APT enabled further assignments of both ^{1}H and ^{13}C spectra to be made.

Recrystallisation of the cycloaddition reaction crude product from acetone-hexane effectively isolated cycloadduct (**2**) without evidence of the by-product (**4**), while recrystallisation of purified material (**2**) from chloroform-methanol gave no reacetylation, implying the absence of acidic species. On the other hand, deliberate acetalisation could

be achieved by exposing a methanolic solution of the cycloadduct (**2**) to toluene-*p*-sulfonic acid (*p*-TsOH) in the presence of molecular sieves.

Scheme 2.3



2 **4**

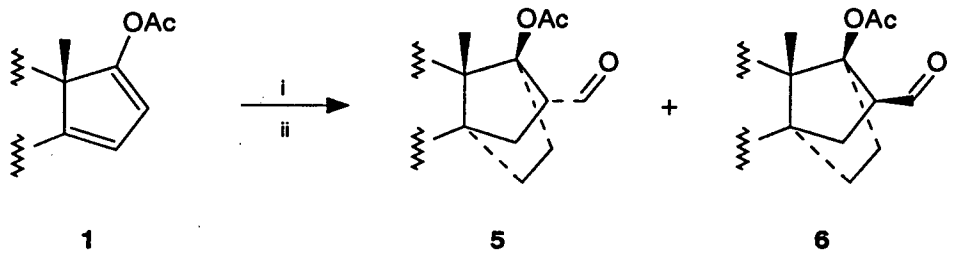
i, MeOH, TsOH; ii, TMSI, CH_2:CMe_2

Deprotection of the dimethyl acetal (**4**) employing trimethylsilyl iodide in chloroform was rapid (30 min at 20°C) and quantitative.[29] The chloroform was initially saturated with isobutylene; the double bond of the isobutylene acts as a scavenger of HI, a by-product which could lead to side reactions in the form of acid-catalysed aldol condensations.

Another route to the target 14β-allyl 17-ketone was also investigated, in which the cycloadduct (**2**) olefinic bond was initially saturated. Palladium-catalysed hydrogenation of the 17^1,17^2-olefinic bond of the cycloadduct (**2**) was complete after *ca* 1 mole hydrogen uptake (90 min); TLC monitoring of the reaction was impaired by the similarity in R_f values of starting material and product. If the total cycloaddition fraction after chromatography was subjected to similar hydrogenation conditions, though, chromatography of the reaction material gave partial separation of two components of similar polarity. The minor component (**6**) was found to be the 17^1,17^2-dihydro analogue of the minor cycloadduct (**3**), which was present as an impurity in the starting material (Scheme 2.4).

The impurity (**6**) was not readily separated from the major component (**5**) owing to their similar R_f values; even recrystallisation techniques failed to completely purify the 16α-carbaldehyde (**5**). It was more practical, therefore, to carry impure material (**5** + **6**) through the following two steps, whereafter a facile separation could be effected.

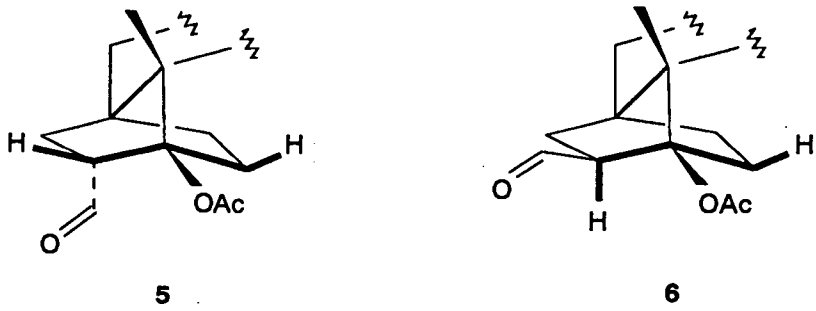
Scheme 2.4



1 5 6

i, Acrolein, BF_3Et_2O; ii, H_2, Pd-C

The mass spectra of the dihydro compounds (**5**) and (**6**) indicated that hydrogenation had occurred (m/z 382). Furthermore, the 16β-proton signal at δ 3.02 (dq, *J* 11.5 and 3 x 3.5 Hz) in the NMR spectrum of **5** was more complex than the analogous doublet of triplets in cycloadduct (**2**), thereby constituting further evidence for the proposed structure of **2**. In the 17^1,17^2-dihydro product, the correct orientation exists for planar four-bond coupling ('W-coupling') between the 16- and 17^1-*exo*- protons (Figure 2.5), thus accounting for the more complex signal in **5**. Such couplings occur between 2,6-removed *exo*-protons in rigid, bicyclic systems, and are of the order of 1-2 Hz.[30] The larger magnitude of the long range coupling in this case may reflect a sterically-crowded environment.



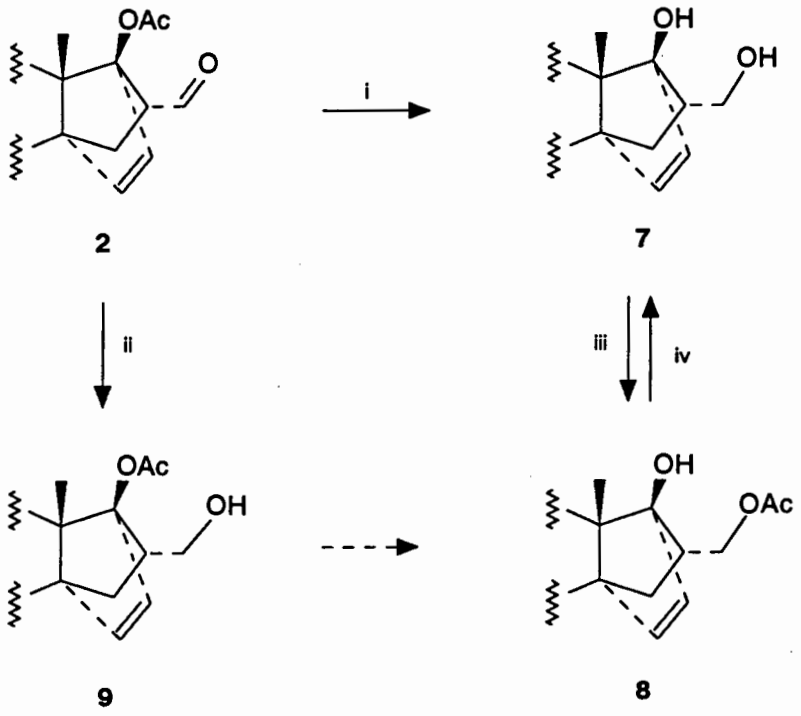
5 6

Figure 2.5: W-coupling in the dihydro compounds (**5**) and (**6**)

On the other hand, the minor product (**6**), when compared with the minor cycloadduct (**3**), did not show any additional splitting due to W-coupling. This is further evidence for the structure proposed for **3** (Figure 2.4). The spectrum of **6** was otherwise comparable to that of **3** except for the absence of the olefinic system AB-pattern found in **3**.

With the cycloadduct (**2**) and its dihydro derivative (**5**) in hand, comparative experiments were carried out in order to establish which of these intermediates would provide the most practical rotue to our objective. Lithium aluminium hydride (LAH) reduction of the etheno compound (**2**) in tetrahydrofuran (THF) at 0°C proceeded readily and cleanly (one component, TLC) to give the expected diol (**7**) (Scheme 2.6).

Scheme 2.6



i, LAH; ii, $NaBH_4$; iii, Ac_2O, pyr; iv, KOH

The diol, however, proved to be extremely insoluble; this explains the low yield (74%) of product finally recovered. Owing to its insolubility in most solvents, complete characterisation of **7** was not possible, and only a mass spectrum was obtained. For characterisation purposes, the diol (**7**) was acetylated (acetic anhydride, pyridine) to give the derived 17β-hydroxy 16^1-acetate (**8**). Infrared absorptions at ν_{max} 3594 and 1728 cm^{-1} confirmed the presence of the -OH and -OAc groups. The NMR spectrum of compound (**8**) displayed signals at δ 3.95 (dd, *J* 10.7 and 6.9 Hz) and 4.04 (dd, *J* 10.7 and 8 Hz) for the diastereotopic 16^1-protons. The 13β-Me signal at δ 0.97 was a doublet (*J* 0.8 Hz), the splitting caused by W-coupling with 12α-H; the presence of this doublet for 13β-Me occurred unpredictably throughout this series. The impracticality of working with the diol (**7**) suggested that use of a milder reductant might be preferable, in order to

ensure survival of the 17β-acetoxy group in the reduction product. Treatment of an ethanolic solution of the cycloadduct (**2**) with sodium borohydride ($NaBH_4$) at 0°C for 90 min proceeded cleanly (one component, TLC). TLC investigation of the total reaction product after work-up, however, indicated the presence of two components. The less polar product (23%) corresponded to the 17β-hydroxy 16^1-acetate (**8**), indicating that the work-up conditions had facilitated transesterification of the desired 16^1-hydroxy 17β-acetate (**9**).

In the ^{1}H-NMR spectrum of hydroxy acetate (**9**), the 16^1-diastereotopic protons resonated at δ 3.36 (ddd, *J* 11.5, 8.5 and 5.4 Hz) and 3.58 (ddd, *J* 11.5, 8.4 and 4.4 Hz). These signals were upfield relative to the equivalent peaks in the spectrum of **8** indicating to the proximity of an hydroxyl group as opposed to the more deshielding 16^1-acetoxy function in **8**. D_2O exchange simplified the 16^1-signals of **9** to doublets of doublets (*J* 11.5 and 8.4, and *J* 11.5 and 5.4 Hz).

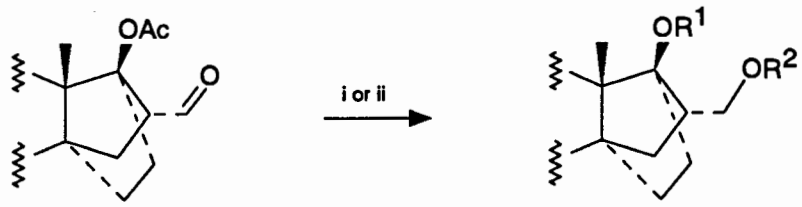
It is known that transesterification is catalysed by traces of acid or base or even by ethyl acetate.[31] Accordingly, various work-up procedures were tested on the borohydride reduction mixture in order to minimise the isomerisation. The most satisfactory method involved pouring the reaction mixture into sufficient saturated aqueous ammonium chloride to precipitate all the material out of solution. The flocculent material was then recovered by rapid filtration under suction. This gave almost exclusively the desired isomer (**9**) in a yield of 89%. This material could be carried through to the next step without further purification. The filtrate was subjected to a usual work-up and chromatographic procedure to isolate further material. The undesired isomer (**8**) isolated in this manner readily underwent hydrolysis in methanolic potassium hydroxide to give the diol (**7**), which could be recycled. Thus, a minimum of material was lost.

The ease with which the interfering reaction proceeded was demonstrated in experiments in which the 17β-hydroxy 16^1-acetate (**9**) was treated with *p*-TsOH in benzene at 20°C for 6h to give the thermodynamically favoured product (**8**). Exposure of **8** to a similar acid treatment resulted in no change to the starting material.

Reduction of the dihydro compound (**5**) with lithium aluminium hydride was performed in a similar manner to that described above (Scheme 2.7). As with the diol (**7**), the product (**10**) was also extremely insoluble, and only mass spectrometric and microanalytical data were obtained by way of characterisation.

Partial reduction of the 16-formyl group of (**5**) was successful in producing the more tractable 16^1-hydroxy 17β-acetate (**11**). No transesterification was noticed at this stage. The spectral characteristics of (**11**) were comparable to those of the dehydro analogue (**9**).

Scheme 2.7



5

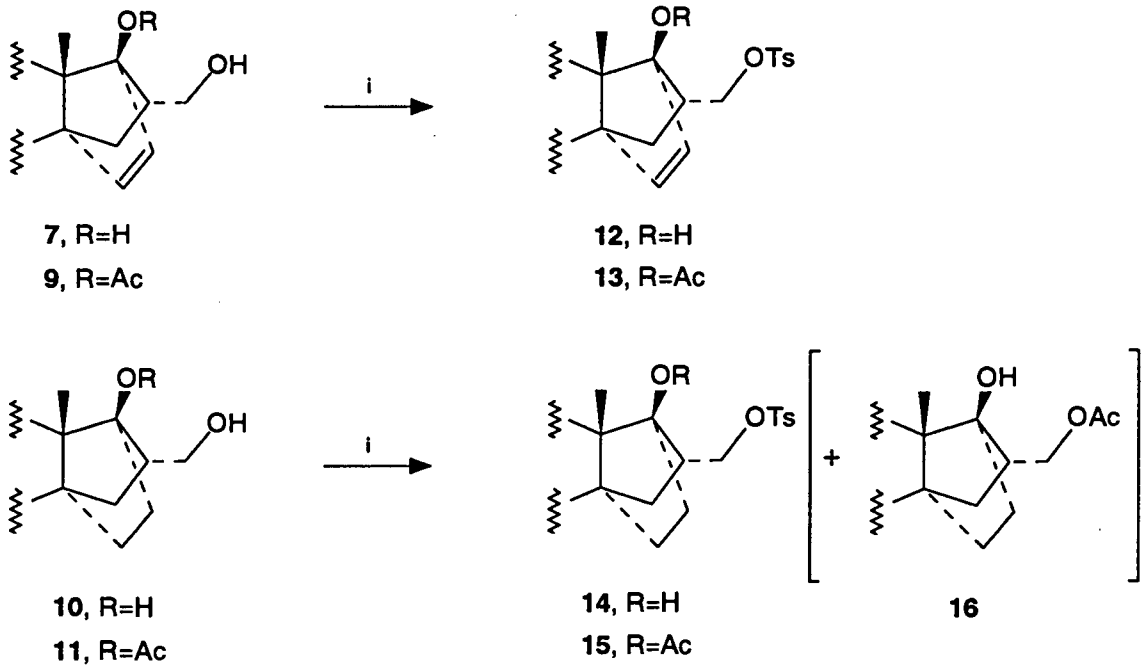
10, $R^1 = R^2 = H$

11, R^1=Ac , R^2 = H

i, LAH, THF; ii, $NaBH_4$, EtOH

The reactions of the 16^1-alcohols **7**, **9**, **10** and **11** with toluene-*p*-sulfonyl chloride (tosyl chloride, TsCl) in pyridine proceeded slowly (24-40 h) at low temperatures (0-7°C). In the case of the diols **7** and **11**, the tosylations were selective as expected. The reactions were uneventful, except in the case of the 16^1-hydroxy 17β-acetate (**11**) where transesterification of the starting material occurred under the conditions employed for tosylation, leading to a depressed yield of the product (**15**) (31%). The unwanted side-product (**16**) was readily recognised from spectroscopic data; treatment of **16** with methanolic potassium hydroxide resulted in a facile conversion to the diol (**10**) (Scheme 2.8).

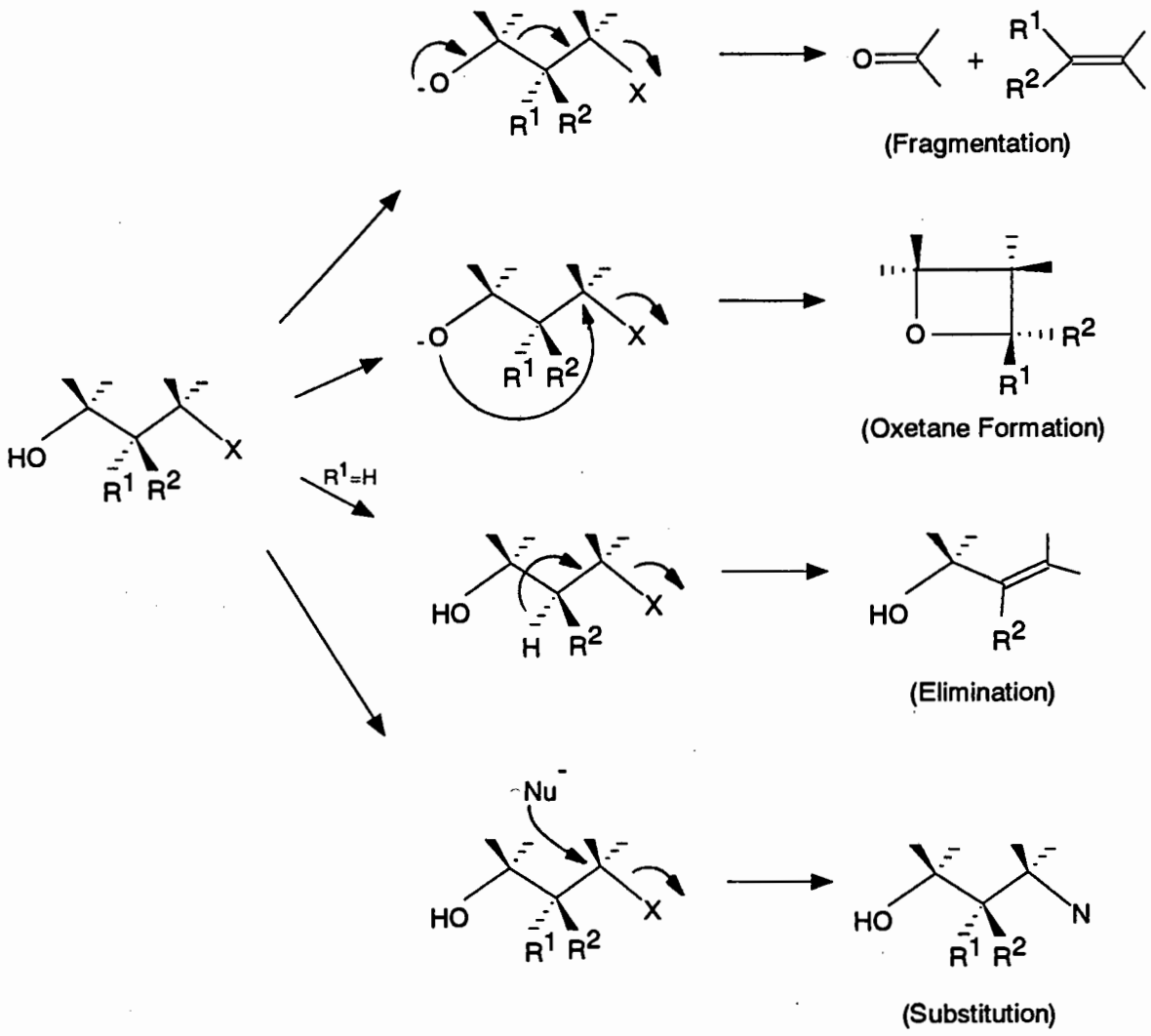
Scheme 2.8



The structural evidence for 17β-hydroxy 16[1]-tosylate (**12**) exemplifies the assignments in this series. The infrared spectrum indicated the presence of a sulfonyl moiety (ν_{max} 1359 and 1174 cm^{-1}), while the tosyl group aromatic protons gave rise to a downfield AB multiplet at δ 7.35 and 7.8 (each d, *J* 8.6 Hz) in the ^{1}H-NMR spectrum of **12**. A quartet of doublets (*J* 3 x 7.9 and 4.4 Hz) at δ 2.5, partially obscured by the aryl-CH_3 group, was assigned to 16β-H by observing a cross-peak with the ABX pattern of the 16[1]-protons in the COSY spectrum. The diastereotopic 16[1]-protons resonated at δ 3.83 and 3.99 (each dd, *J* 9.4 and 7.9 Hz), while the etheno-bridge protons occurred as the expected AB multiplet at δ 5.7 and 6.01 (each d, *J* 6.2 Hz).

Heterolytic fragmentations of cyclic 1,3-removed diol derivatives are known as Wharton fragmentations.[24] The alkoxide produced upon deprotonation of a 1,3-diol derivative may undergo concerted fragmentation to give carbonyl and olefinic functionality, provided an *anti*, but not necessarily antiperiplanar, relationship exists between the two bonds undergoing cleavage (Scheme 2.9). Other possible reaction outcomes would be oxetane formation, elimination of *p*-TsOH, and substitution of the tosyl group.

Scheme 2.9



The 1,3-removed 17β-alkoxy 16[1]-tosylate systems (**12-15**) were appropriately set up for Wharton fragmentation to succeed. Oxetane formation could be excluded as a side reaction in view of the enormous ring-strain this would invoke (Figure 2.10). Models could not, however, predict whether elimination or substitiution reactions would interfere.

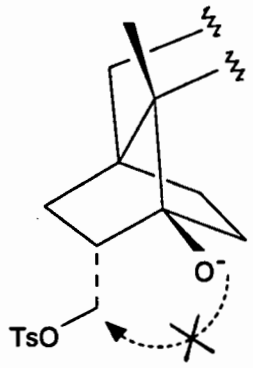
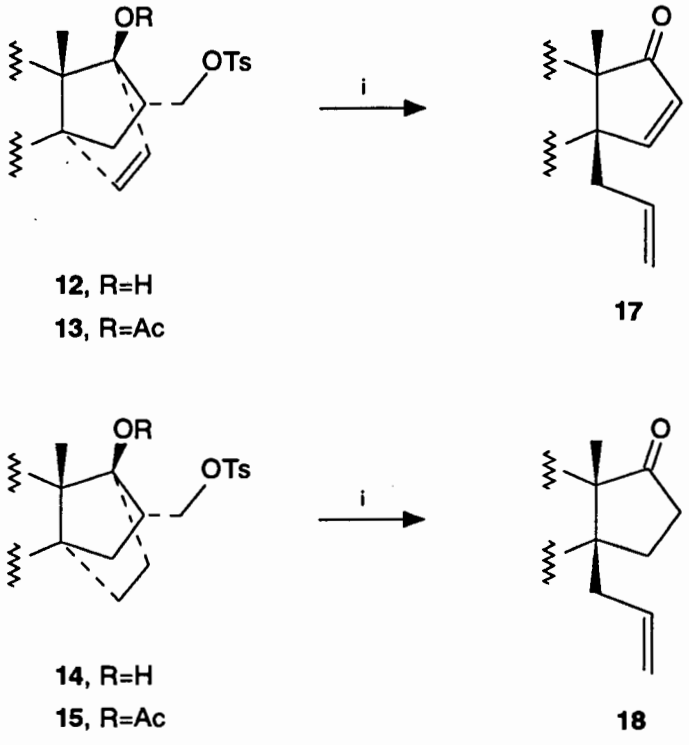


Figure 2.10: Oxetane formation pathway

The rate of fragmentation depends on the concentration of the anion; consequently, stronger and less nucleophilic bases tend to favour fragmentation pathways. Treatment of hydroxy tosylate (**12**) with methanolic potassium hydroxide at 20°C for 1 h led to quantitative yields of the desired 14β-allyl enone (**17**) (Scheme 2.11).

Scheme 2.11



The infrared spectrum of **17** showed a carbonyl absorption band at ν_{max} 1701 cm^{-1}, as expected for a cyclopentenone carbonyl group.[30] Furthermore, the uv spectrum demonstrated the presence of this chromophore (λ_{max} 245 nm for a $\pi \rightarrow \pi^*$ transition, and a weak $n \rightarrow \pi^*$ transition at λ_{max} 325 nm). The 400 MHz ^{1}H-NMR spectrum of allyl ketone (**17**) was consistent with the proposed structure; with the aid of COSY, HETCOR, DEPT and ^{13}C data, it was possible to assign the spectrum fully (Figure 2.12).

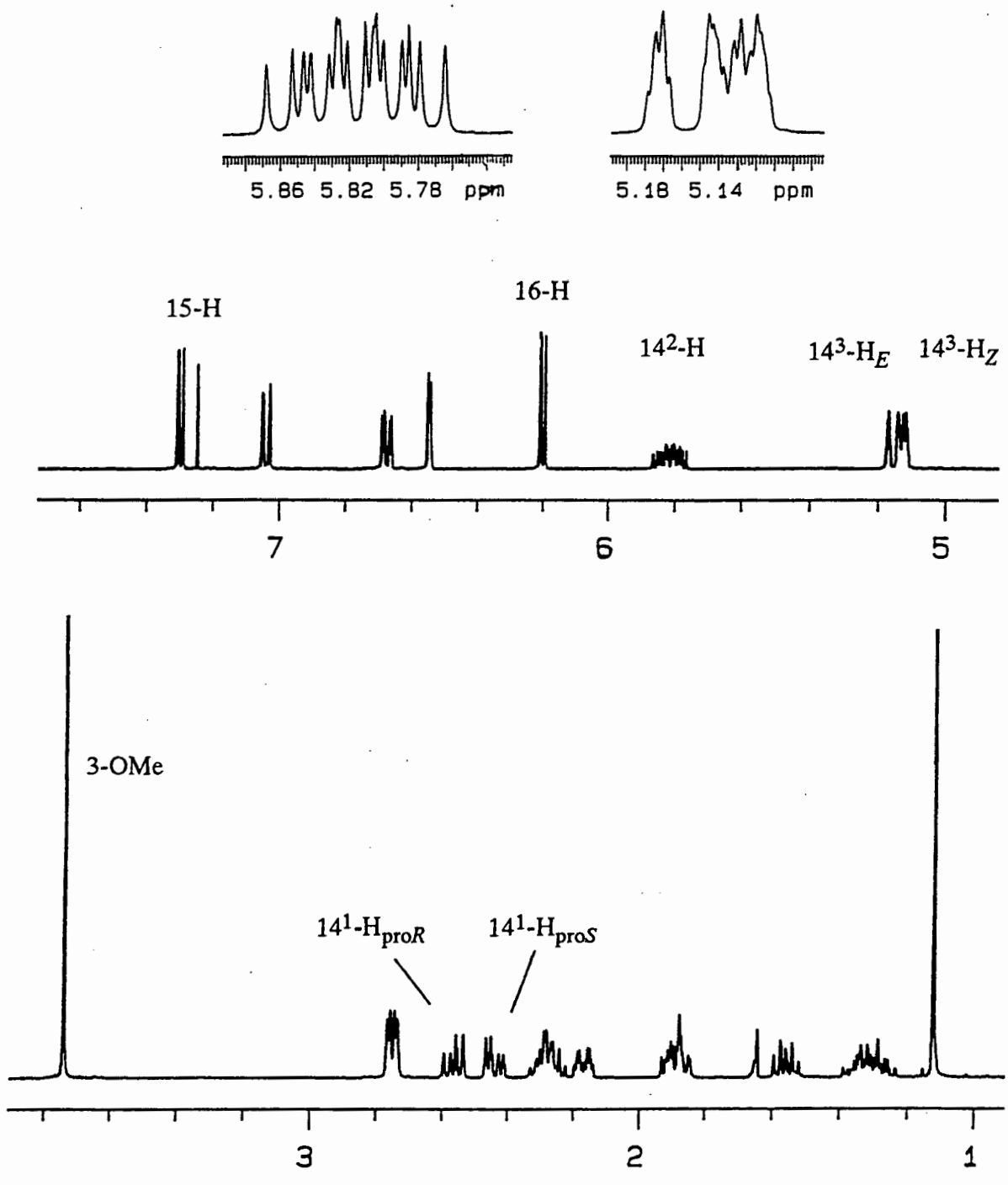
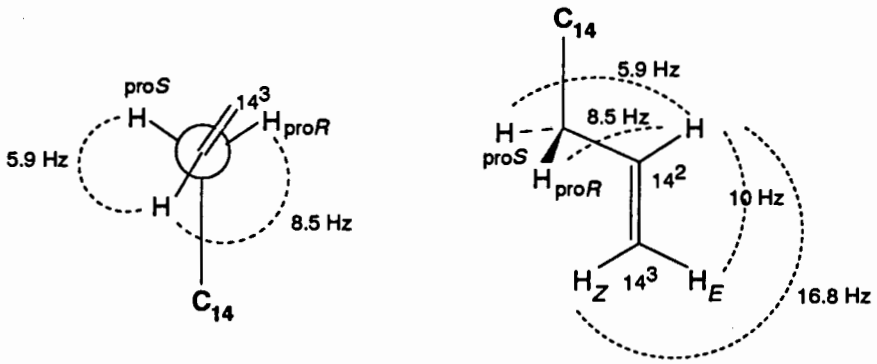


Figure 2.12: 400 MHz NMR Spectrum of the 14β-Allyl 17-Ketone (**17**)

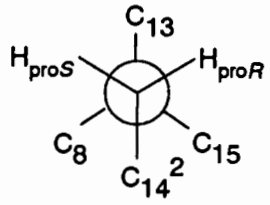
Table 2.13: NMR Assignments for the 14β-Allyl 17-Ketone (**17**)

δ /ppm	Integration, Multiplicity, Assignment
1.12	3H, s, 13β-Me
1.26	1H, m, 7α-H
1.35	1H, m, 11β-H
1.56	1H, dt, *J* 13.8 and 2 x 7.9 Hz, 12α-H
1.86	1H, m, 12β-H
1.91	1H, m, 8β-H
2.17	1H, dq, *J* 12.4 and 3 x 2.4 Hz, 7β-H
2.26	1H, m, 11α-H
2.31	1H, m, 9α-H
2.44	1H, ddt, *J* 15, 5.9 & 2 x 1.5 Hz, 14^1-H_{proS}
2.56	1H, dd, *J* 15 and 8.5 Hz, 14^1-H_{proR}
2.75	2H, dd, *J* 8.4 and 3.6 Hz, 6-H_2
3.74	3H, s, 3-OMe
5.13	1H, br d, $W_{1/2}$ 7 Hz, 14^3-H_Z
5.16	1H, ddd, *J* 10.2, 3.2 and 1.5 Hz, 14^3-H_E
5.82	1H, dddd, *J* 16.8, 10.2, 8.5, 5.9 Hz, 14^2-H
6.20	1H, d, *J* 5.8 Hz, 16-H
6.55	1H, d, *J* 2.7 Hz, 4-H
6.68	1H, dd, *J* 8.7 and 2.7 Hz, 2-H
7.04	1H, d, *J* 8.7 Hz, 1-H
7.31	1H, d, *J* 5.8 Hz, 15-H

The signal at δ 5.16 (ddd, *J* 10.2, 3.2 and 1.5 Hz) was assigned to the 14^3-H_E in accordance with the 7-10 Hz coupling to 14^2-H expected for *cis*-related olefinic protons, with a vicinal coupling to the other 14^3-H_Z of 3.2 Hz, and a 4-bond coupling to one of the 14^1-protons (*J* 1.5 Hz). The 14^3-H_Z was not as resolved.The signal at δ 5.82 for 14^2-H was a well-resolved dddd (*J* 16.8, 10.2, 8.5 and 5.9 Hz). The large coupling (*J* 16.8 Hz) is consistent with the *trans*-disposition of the 14^2- and 14^3-H_Z. The smaller couplings (*J* 8.5 and 5.9 Hz) arose from vicinal interactions with the 14^1-protons. The fact that these couplings are non-equivalent indicated that the orientation around C(14)-C(14^1) is not fully symmetrical. The pro-*S* 14^1-H has a smaller dihedral angle with respect to 14^2-H, and hence a smaller coupling constant (Figure 2.14).



$C(14^2)$ - $C(14^1)$ projection



$C(14^1)$ - C(14) projection

Figure 2.14: Orientation of the 14β-allyl group

The pro-*S* 14^1-H signal indicated the presence of two long-range couplings (each *J* 1.5 Hz), whereas the diastereomeric 14^1-H only experienced geminal and vicinal couplings. A crosspeak in the COSY spectrum identified one of the four-bond couplings as that between 14^1-H_{proS} and 14^3-H_E. No further crosspeaks were found in the COSY spectrum to indicate which proton was the other four-bond coupling partner. From models, the alignment between 14^1-H and 15-H is closer to an extended W than between 14^1-H and 8β-H, but the 1.5 Hz coupling was not reflected in the clean 15-H signal (d, *J* 5.8 Hz). The four-bond coupling between 14^3-H_Z and 14^1-H_{proS} is also a coupling candidate.

The 17β-acetoxy 16^1-tosylate (**13**) gave a similar reaction outcome to that described for hydroxy tosylate (**12**) under similar reaction conditions. Further experiments were conducted on the dihydro series (**14**) and (**15**), giving rise to fragmentation to the 14β-allyl 17-ketone (**18**) in quantitative yield. The spectral characteristics of the ketone (**18**) were comparable to those of the enone (**17**), except for the absence of the olefinic proton signals. The NMR spectrum of the dihydro compound

(**18**) was useful in assisting with the assignments for **17** owing to improved resolution with respect to certain signals.

The most notable difference in the two series (dehydro *vs* dihydro) was the rate of fragmentation. The hydroxy tosylate (**12**) required only ambient temperatures and 1 h to fragment to the allyl enone (**17**), whereas the dihydro analogue (**14**) required heating (50°C) and longer reaction time (3 h) to fragment to the allyl ketone (**18**). Fragmentation was thus accelerated in the presence of the olefinic bond, probably because it was driven by the stabilising influence of the resultant α,β-unsaturated carbonyl system in the product.

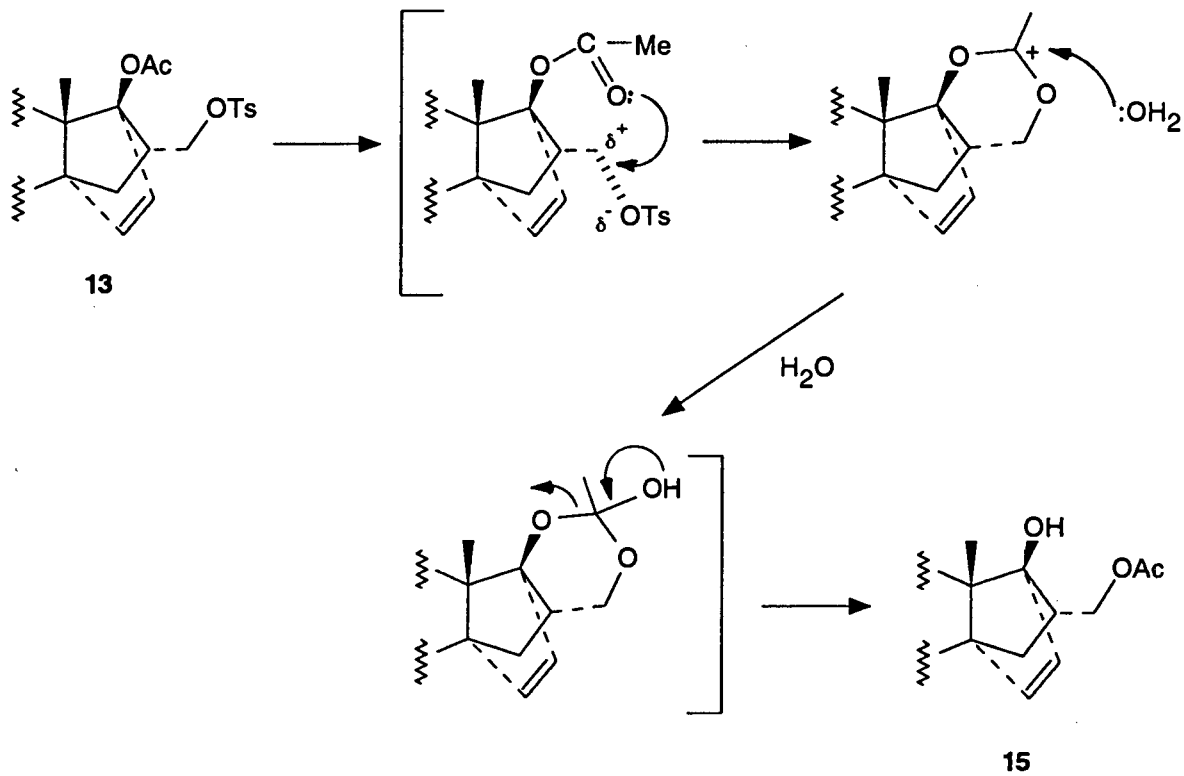
This fragmentation reaction was a key step in the synthetic route, constituting a stereocontrolled method for the introduction of the 14β-allyl group with concomitant restoration of the D-ring.

Further interest in this reaction series was the evidence for an exclusive fragmentation pathway under the reaction conditions. There was no sign of non-fragmentation by-products under the conditions employed (KOH/MeOH). One such by-product, namely that of elimination, was of interest as a possible intermediate in unrelated investigations, and an attempt was made to synthesise it deliberately by treating the 16^1-tosylates with a non-nucleophilic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The hydroxy tosylates (**12**) and (**14**) both underwent fragmentation on reaction with DBU, to form the allyl enone (**17**) and allyl ketone (**18**) respectively. DBU is not known to hydrolyse bridgehead esters; in an attempt to block fragmentation and thereby promote elimination to the desired 16-methylene compounds, the 17β-acetoxy 16^1-tosylates (**13**) and (**15**) were exploited as substrates. Prolonged treatment of the dehydro compound (**13**) with DBU in refluxing toluene for 40 h, however, gave rise mainly to the acetoxy alcohol (**8**) (59%), along with a small amount of the allyl enone (**17**) (5%). The acetoxy tosylate (**15**) required 20 h of exposure to DBU in refluxing toluene to form the acetoxy alcohol (**16**). The formation of these rearrangement products can only be explained by an intramolecular participation reaction involving acyl transfer from C(17) to C(16^1) (illustrated for compound **13**, Scheme 2.15).[32]

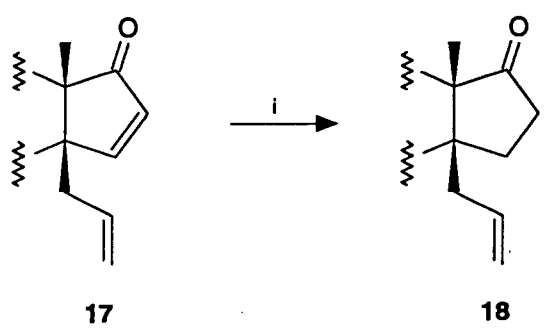
The foregoing parallel investigation involving conversion of both the cycloadduct (**2**) and its dihydro derivative (**5**) into the allyl enone (**17**) and the allyl ketone (**18**) respectively, was conducted for comparative purposes. In practice, our preference was to adopt the former route, since the intermediates proved to be experimentally more tractable and highly crystalline (thereby assisting purification and characterisation). It was further demonstrated that the allyl enone (**17**) underwent highly effective and chemoselective reduction to the allyl ketone (**18**). The method of choice for this purpose was the recently described procedure involving exploitation of the novel reducing reactivity of diisobutylaluminium hydride (DIBAH) modified by a catalytic amount of

methylcopper (MeCu), which was prepared *in situ* from an equimolar reaction between methyllithium and copper(I) iodide.[33] The reduction occurred rapidly and selectively at -70°C, to give the allyl ketone (**18**) in 82% yield (Scheme 2.16).

Scheme 2.15



Scheme 2.16



i, MeLi, CuI, HMPA, DIBAH

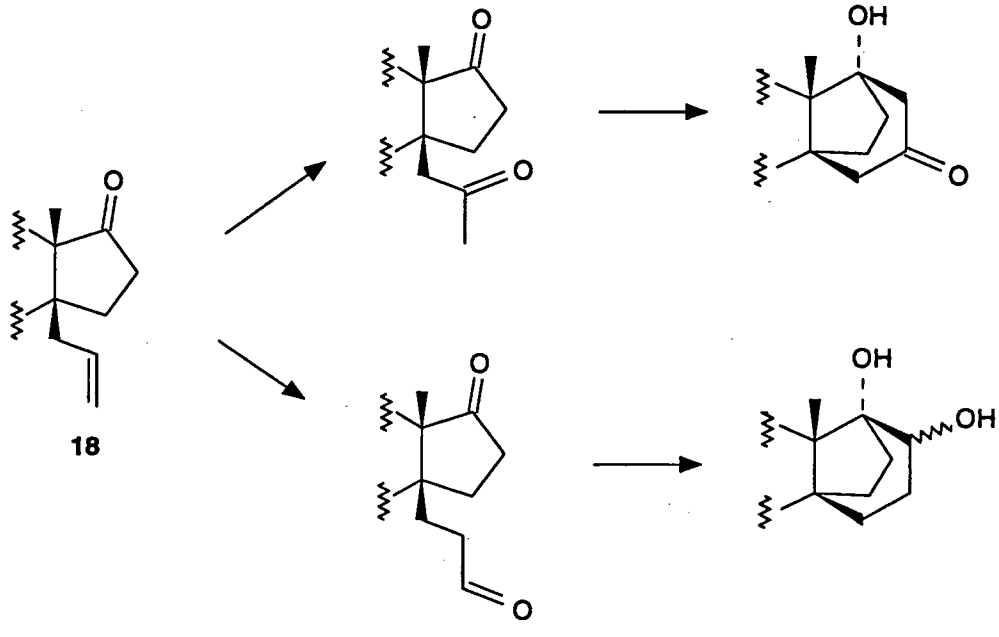
Chapter 3

SYNTHESIS OF 14β,17β-PROPANOESTRATRIENES

3.1 General Objectives

With the 14β-allyl 17-ketone (**18**) in hand, we were now in a position to undertake the regioselective oxidation of the 14β-allyl moiety with the aim of introducing functionality for intramolecular coupling with the 17-oxo group. Oxidation of the allyl group under Wacker conditions was expected to give rise to the 14β-acetonyl 17-ketone exclusively. Intramolecular aldol condensation of the diketone would provide access to the 14β,17β-propano bridged series of compounds; reduction of the residual 17^{2}-carbonyl group would then lead to the parent hormone, possessing the definitive 17-hydroxy functionality required of an estradiol. If the 14^{3}-position of the 14β-allyl group was oxidised, however, a reductive coupling between the two carbonyl groups could be envisaged, giving rise to 14β,17β-propano-bridged 17^{1}-'estriol' analogues. The most direct route to the 14β-formylethyl 17-ketone appeared to involve hydroboration-oxidation of the olefinic bond of the 14β-allyl substituent, followed by careful oxidation of the primary alcohol to the aldehyde (Scheme 3.1).

Scheme 3.1

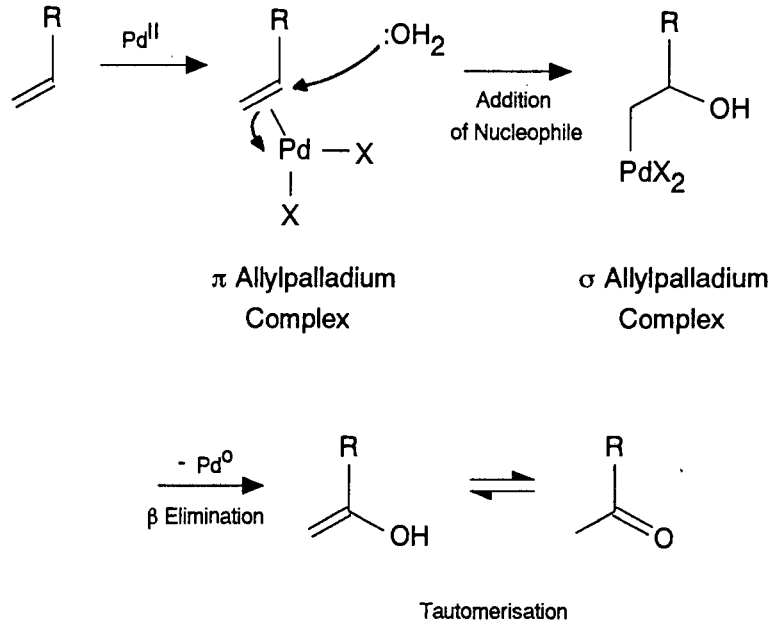


These approaches were essentially complementary, since either of the closure products could be expected to lead, via chemoselective deoxygenation, to the 14β,17β-propano analogues of estradiol. Furthermore, access would also be provided to bridged analogues having additional hydroxy functionality at C(17^1) and C(17^2), which could be regarded as spatial variants of estradiol. The presence of functionality in the bridge would also provide scope for further structural modifications in this series of hormone analogues.

3.2 14,17β-Propano-14β-estra-1,3,5(10)-triene-3,17α-diol

The oxidation of ethylene to acetaldehyde using palladium(II) chloride and copper(II) chloride as catalysts under an oxygen atmosphere is well known as the Wacker process.[34] The key step is Markovnikof hydration of the palladium(II)-complexed double bond (Scheme 3.2). As expected from the regioselectivity of palladium(II)-assisted addition of nucleophiles to alkenes, simple terminal olefins are converted into methyl ketones rather than into aldehydes.[35]

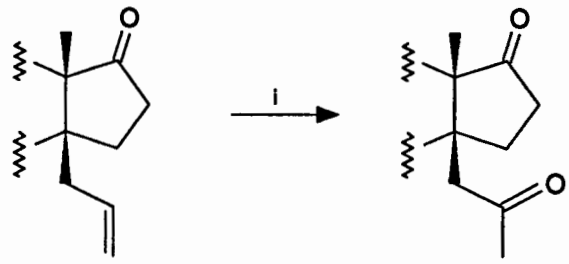
Scheme 3.2



It was found to be necessary to stir the $PdCl_2$-CuCl catalyst system in the solvent (dimethylformamide-water) for 3 h under an oxygen atmosphere prior to adding the allyl ketone (**18**) in order to fully oxidise the Cu(I) species to the Cu(II) species, which would

then serve to reoxidise the palladium catalyst after it was reduced in the catalytic cycle. This reaction was relatively clean, fast and reproducible, and gave a 70% yield of the 14β-acetonyl 17-ketone (**19**) (Scheme 3.3).

Scheme 3.3



18 **19**

i, O_2, $PdCl_2$, CuCl

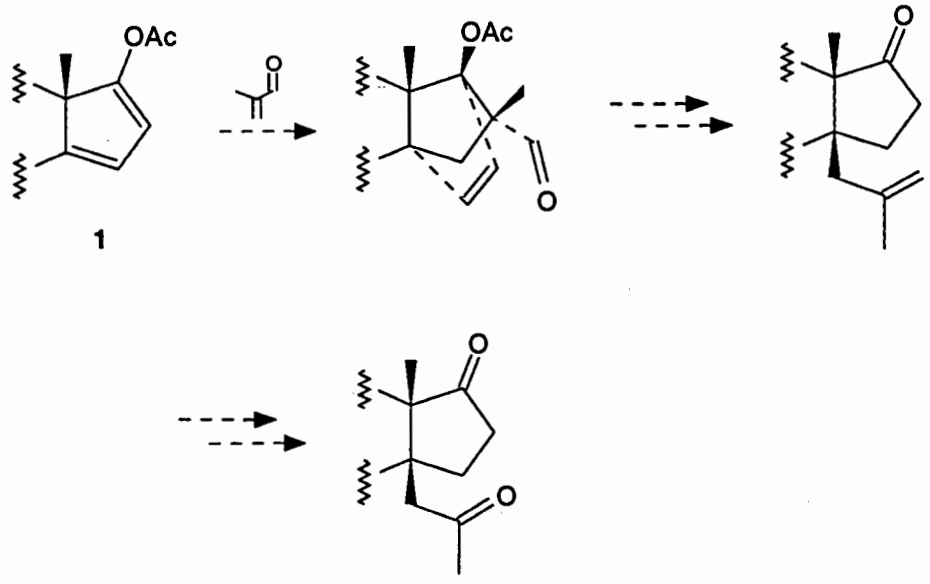
The infrared spectrum of the oxidised compound (**19**) showed a broad absorption band at ν_{max} 1726 cm^{-1} for the carbonyl groups, and the molecular ion confirmed the addition of oxygen. The 14^3-protons resonated as a high-field (δ 2.15) singlet in the NMR spectrum, and an AB multiplet at δ 2.39 and 2.62 (each 1H, *J* 17.2 Hz) was assigned to the 14^1-protons. Full characterisation of **19** was not possible owing to its lack of crystallinity.

The initial induction period in the Wacker oxidation procedure, during which time the reagent was generated, was found to be essential. Reactions in which this step was omitted, failed. In an attempt to better the 70% yield, alternative methods were investigated, such as the use of palladium acetate as catalyst with hydrogen peroxide as the oxygen source.[36] This reaction was incomplete and unselective (TLC); the peroxide probably decomposed too rapidly at the elevated temperature required (80°C). Another procedure utilised a multi-step catalytic cycle involving iron phthalocyanine, palladium acetate, hydroquinone and perchloric acid under an oxygen atmosphere.[37] This reaction also gave rise to a multi-component mixture (TLC), and 26% was the highest yield of diketone (**19**) obtained. Another possible route involved epoxidation of the allyl olefinic bond, followed by rearrangement of the epoxide to the acetonyl ketone (**19**).[38] *m*-Chloroperbenzoic acid epoxidations in chloroform, dichloromethane and tetrahydrofuran, in both buffered and unbuffered media all gave rise to multicomponent mixtures, none going to completion. This route was thus abandoned.

Consideration was also given to the possibility of modifying the initial cycloaddition step in order to generate fragmentation products which would undergo

regiodefined modifications to a 14β-acetonyl group. Thus, it was reasoned that cycloaddition of methacrolein or methyl methacrylate would give intermediates for reduction-tosylation-fragmentation, leading to 14β-(2-methylpropenyl) 17-ketones. Oxidative cleavage of the 14^2-methylene moiety would then provide the 14β-acetonyl 17-ketone (**19**) (illustrated for methacrolein, Scheme 3.4). The dienyl acetate (**1**), however, failed to react with methacrolein in toluene using either boron-triflouride diethyl ether complex as a Lewis acid catalyst or employing thermal conditions in a sealed tube. Methyl methacrylate similarly resisted cycloaddition. This result was unsurprising considering the knowledge that the 13β-methyl group is a sterically impeding group towards cycloadditions.[39] Monofunctionalised or unbranched dienophiles have proved successful, whereas branched or α-functionalised dienophiles are considerably more difficult to cycloadd to this diene (**1**).

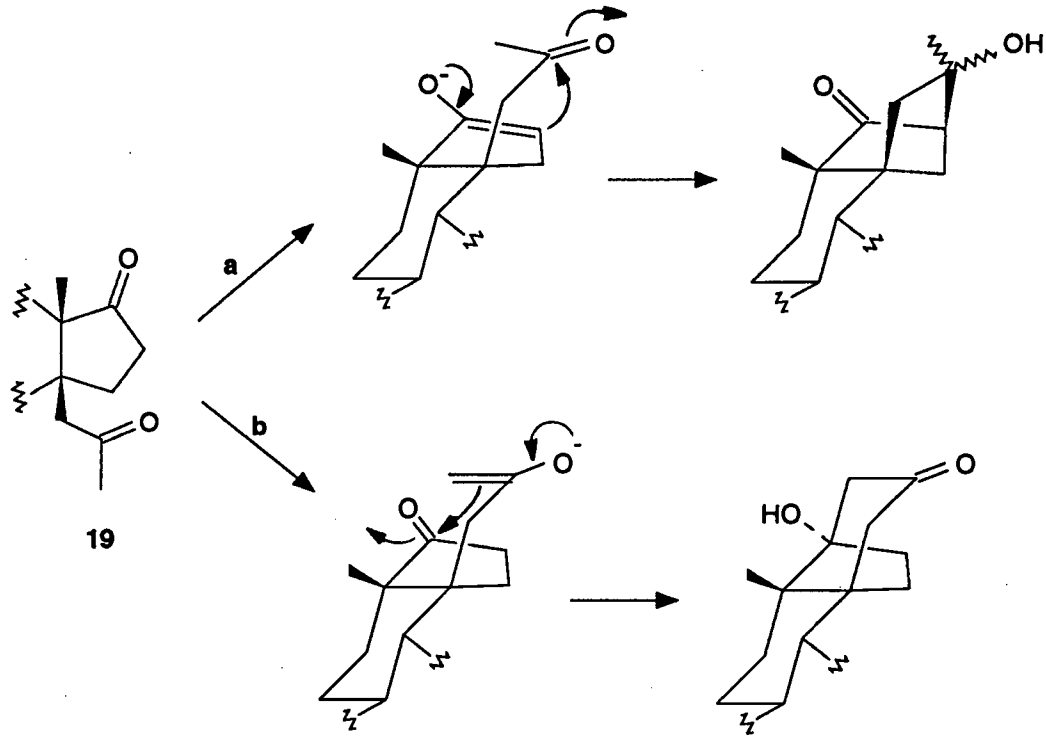
Scheme 3.4



1 **19**

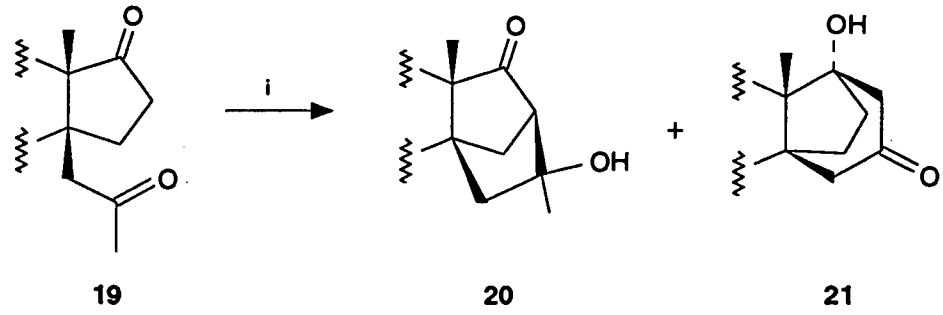
The lack of success in oxidising the allyl group using other procedures indicated that the Wacker oxidation was the route of choice. Base treatment of diketone (**19**) was expected to give rise to the first key compound in this study towards the synthesis of 14β,17β-propano 19-norsteroids. The orientation of the functional groups involved in the transannular intramolecular aldol condensation, forming chair-like six-membered ring transition states, indicated that closure should occur readily.[40] The direction of enolisation in the transition state was, however, uncertain, as was the distereoselectivity. The two modes of closure possible with this system are depicted in Scheme 3.5.

Scheme 3.5



Treatment of a THF solution of the diketone (**19**) with an excess of methanolic potassium hydroxide at 20°C for 30 min gave 17α-hydroxy-3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17[2]-one (**21**) in 70% yield. A small amount (*ca* 6%) of the undesired aldol closure product (**20**) was also formed (Scheme 3.6).

Scheme 3.6



i, KOH, MeOH

The spectral data obtained for **21** supported the proposed 17α-hydroxy 17^2-ketone structure. The infrared spectrum showed absorption bands at ν_{max} 3596 cm^{-1} (OH), and 1707 cm^{-1} (cyclohexanone carbonyl group). The two expected AB multiplets for the 17^1- and 17^3- protons were located by crosspeaks in the COSY and HETCOR spectra in the high-field region of the ^{1}H-NMR spectrum. The 17^1-protons resonated at δ 2.49 (dd, *J* 17.4 and 2 Hz, 17^1α-H) and 2.8 (dd, *J* 17.4 and 2.8 Hz, 17^1β-H), while the 17^3-signals were found at δ 2.2 (dd, *J* 17.4 and 2.6 Hz, 17^3α-H) and 2.51 (dd, *J* 17.4 and 2 Hz, 17^3β-H), the stereochemistry assigned on the basis of the relative deshielding of axial protons with respect to the equatorial protons in a cyclohexanone system. The smaller (2-2.8 Hz) couplings must be caused by four-bond couplings. From models, it would appear that 17^1β-H forms a W with 16-H_{exo} (*J* 2.8 Hz), as does 17^3β-H with 15-H_{exo} (*J* 2.6 Hz). The 17^1- and 17^3-α protons also have a W-orientation relative to each other (*J* 2 Hz) (Figure 3.7).

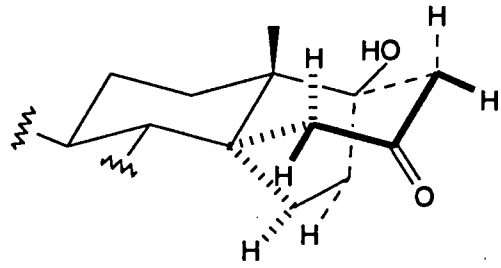
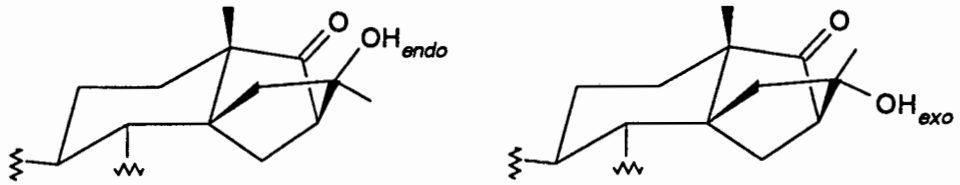


Figure 3.7: W-Coupling in the hydroxy ketone (**21**)

The infrared spectrum of the minor product (**20**) showed absorption bands at ν_{max} 1733 cm^{-1} consistent with a cyclopentanone carbonyl group, and 3584 cm^{-1} (OH). The ^{1}H-NMR spectrum showed **20** to be an inseparable mixture of isomers in approximately a 1:2 ratio, according to the relative intensities of the two sets of methyl signals (*viz.* 13β- and 16^1-Me). The configuration at C(16^1) was suggested by the chemical shift differences of these methyl singlets. The major epimer was assigned the configuration with the 16^1-methyl group having an *endo*-disposition (Figure 3.8). The *endo*-16^1 hydroxy group and the 13β-methyl substituent share a 1,3 syn-diaxial interaction, this inducing slight deshielding of the 13β-methyl signal (δ 1.16). The 13β-Me group in the unsubstituted 14β,16β-ethano 17-ketone, synthesised by Thomson,[41] resonated at δ 1.05, comparable to that for the minor epimer (δ 1.04), in which case the 16^1-hydroxy group is not influencing the 13β-Me chemical shift.



Major epimer of (**20**)

Minor epimer of (**20**)

Figure 3.8: Epimers of the 14,16β-ethano 17-ketone (**20**)

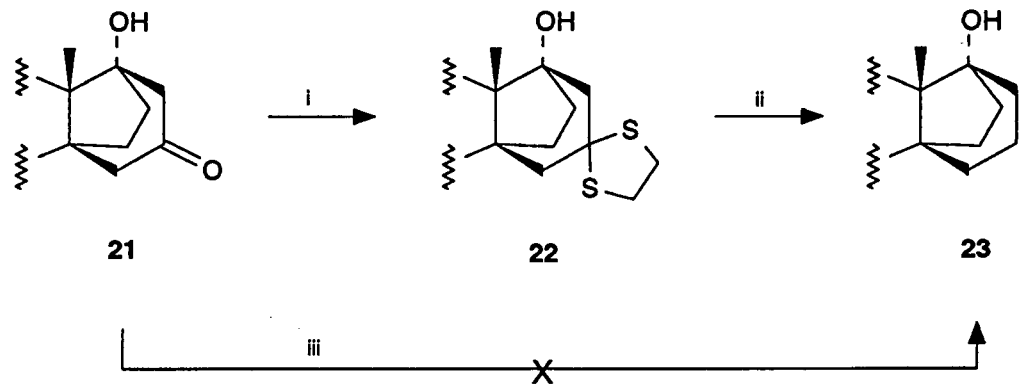
Completion of the synthesis of the 14β,17β-propano analogue of estradiol necessitated deoxygenation of the aldol condensation product (**21**) at C(17^2). An attempt to conduct this step directly via Wolff-Kishner reduction of **21** was unsuccessful, since conventional treatment of the hydroxy ketone (**21**) with hydrazine hydrate, diethylene glycol, and potassium hydroxide gave rise to a complex mixture of polar products. It is possible that retroaldolisation under the reaction conditions may account for the result. Accordingly, a milder method of deoxygenation was sought in order to avoid retroaldol cleavage of the new bridge, and a thioketalisation-desulfurisation route was examined.

A particularly mild method of catalysis using zinc trifluoromethanesulfonate (zinc triflate) in the thioketalisation step has recently been reported, and was applied here.[42] Treatment of a dichloromethane solution of the hydroxy ketone (**21**) with ethane-1,2-dithiol and catalytic zinc triflate gave clean, quantitative, and rapid (3.5 h) 17^2,17^2-dithioketalisation (Scheme 3.9).

The ^{1}H-NMR spectrum of the product (**22**) showed the 17^2,17^2-dithioketal group as a four-proton multiplet in the 3.24-3.46 ppm region, and the mass spectrum confirmed that thioketalisation had taken place.

It was subsequently found that thioketalisation proceeded as efficiently, but not as rapidly (8 h) when the reaction was conducted with ethane-1,2-dithiol in glacial acetic acid in the presence of catalytic *p*-TsOH.[43] Thioketalisation with neat ethanedithiol using boron trifluoride-diethyl ether complex as catalyst proceeded rapidly (15 min), but gave rise to two components comprising thioketal (**22**) and an unidentified compound. If THF was employed as a solvent, the reaction was slower and incomplete, but only the desired product (**22**) was formed.

Scheme 3.9



i, $HS(CH_2)_2SH$, cat.; ii, Raney Ni; iii, Wolff-Kishner

Desulfurisation of the $17^2,17^2$-dithioketal (**22**) was performed with commercially available Raney nickel (Aldrich, W2) in ethanol under reflux.[44] The reaction was clean and rapid (3 h) and proceeded in high yield (95%) to form 3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17α-ol (**23**). As expected, the ^{1}H-NMR spectrum of this product (**23**) lacked any definitive downfield signals, which was compatible with the assigned structure, as was other spectroscopic and analytical data.

A single-crystal X-ray structure determination was performed on (**23**) (see Chapter 8 for crystal data) (Figure 3.10). The crystal structure displayed no unexpected structural or conformational features. Thus, rings A, B and C showed characteristics typical of the estra-1,3,5(10)-triene skeleton. It is of interest to note that in this series, the conformation of ring-B may be a 7α,8β-half chair ($^8H_7$) or an 8β-envelope (^8E), and in this instance the former is preferred. Ring C is a chair ($^8C_{12}$) and ring D is an envelope (E_{13}). This is typical of 14β-steroids.[45] The bridged 14β,17β-propano moiety constitutes part of an unstrained cyclohexanoid element ie. the new bridging ring [C(13)-C(14)-$C(17^3)$-$C(17^2)$-$C(17^1)$-C(17)] is a chair ($^{13}C_{17^2}$).

In general, the 7α,8β-half chair conformation for ring B is favoured in 1,3,5(10)-estratriene structures.[46] However, most of the conformational flexibility in this steroid backbone is located in the B-ring. Thus, this ring has also been observed as an 8β-envelope, which constitutes a generally less favourable conformation than the ideal half-chair because it requires near eclipsing of the C(1)-C(10) and C(9)-C(11) bonds. Numerous structural and molecular mechanics studies have demonstrated that energy barrier between the two conformers of ring-B is very small.[46] In some structures (eg. estradiol, estrone, epiestradiol) the 8β-envelope conformer is of comparable stability to the half-chair.

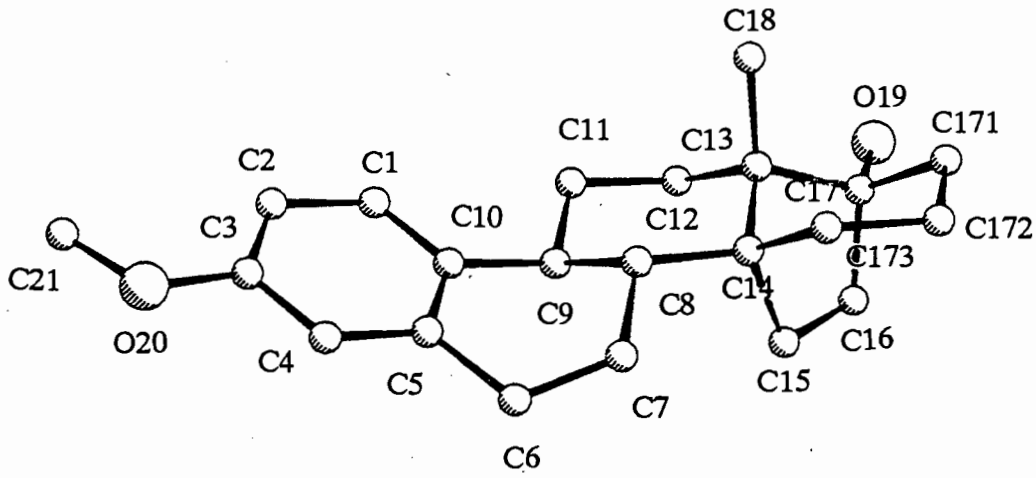
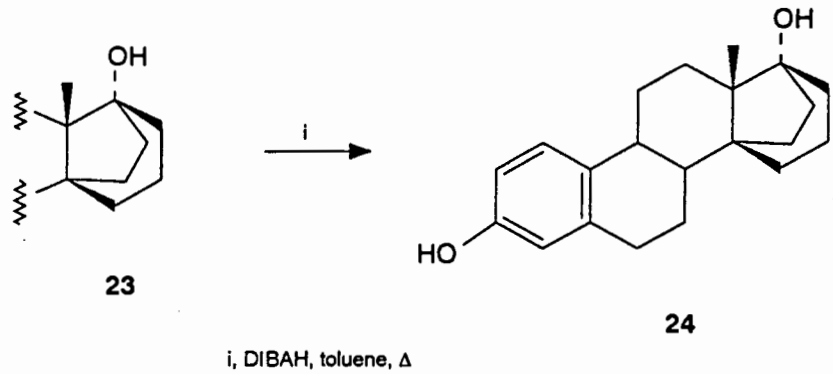


Figure 3.10: X-ray Crystal Structure of Alcohol (**23**) Showing Crystallographic Numbering

Treatment of the reduced compound (**23**) with diisobutylaluminium hydride (DIBAH) in refluxing toluene for 24 h resulted in deprotection of the 3-position (Scheme 3.11).

Scheme 3.11



23 **24**

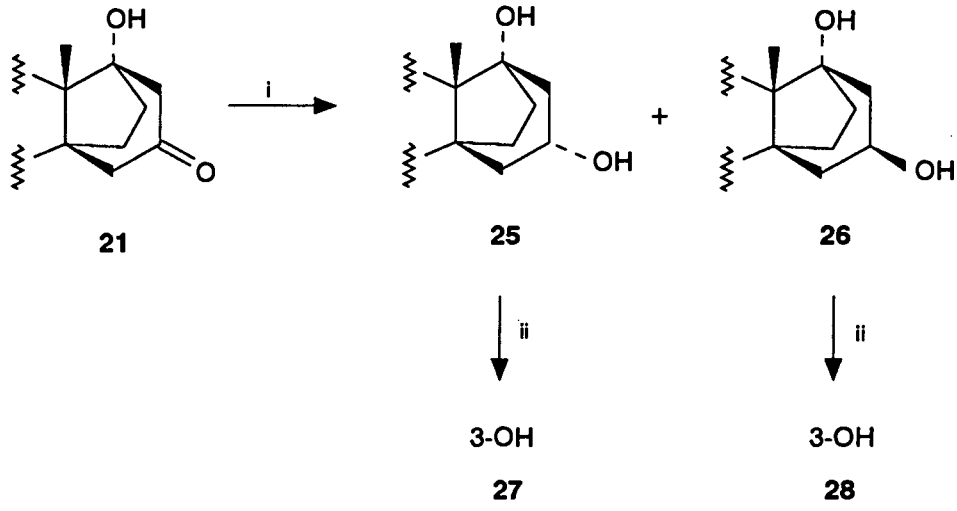
i, DIBAH, toluene, Δ

The diol (**24**) was formed quantitatively. Owing to the insolubility of the product in most solvents, full characterisation was not possible, but analytical data were consistent with the structure. This compound was submitted for biological evaluation as an estrogen analogue.

3.3 Functional Variants of the Bridged Estradiol

Synthesis of the 17^2-'estriol' analogues. The product of aldol condensation was an ideal substrate for synthetic access to the 17^2-'estriol' analogues of estradiol **24**. Treatment of 17α-hydroxy-3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17-one (**21**) with lithium aluminium hydride in tetrahydrofuran at 0°C for 1 h, gave rise to two chromatographically-separable diols (**25**) and (**26**) in a 1:1.6 ratio (Scheme 3.12).

Scheme 3.12



i, LAH, THF; ii, DIBAH, toluene, Δ

The 17^2-proton of the minor epimer (**25**) resonated as a triplet (J 2 x 6.2 Hz) at δ 4.27 in the ^{1}H-NMR spectrum . The signal width (12.4 Hz) was compatible with a 17^2-*exo* proton. A triplet of triplets (J 2 x 10.5 and 2 x 7.4 Hz) at δ 4.04 was assigned to 17^2-H_n of the major epimer (**26**), the signal width (35.8 Hz) being in agreement with two large $J_{ax\text{-}ax}$ and two smaller $J_{ax\text{-}eq}$ couplings. The symmetry of the 17^2-H signals for both epimers was indicative of a chair conformation in the six-membered ring.

The fact that both isomers (**25** and **26**) were formed on LAH reduction is unsurprising for the bicyclo[3.2.1] octanone system under investigation. Use of a more hindered hydride would improve the stereoselectivity, giving rise to *exo*-attack of the carbonyl group. It was, however, convenient to obtain both isomers of reduction in a single step.

Both diols (**25** and **26**) were demethylated in the conventional manner (DIBAH, refluxing toluene) and the respective 17^2-'estriols' (**27**) and (**28**), submitted for biological evaluation.

Introduction of Unsaturation. With the availability of the aldol condensation product (**21**), it was logical to exploit the 17^2-functionality to introduce unsaturation into the 14β,17β-propano bridge using Shapiro methodology. In view of the symmetrical environment about the 17^2-carbonyl group, it was uncertain as to whether there would be any regioselectivity of elimination.

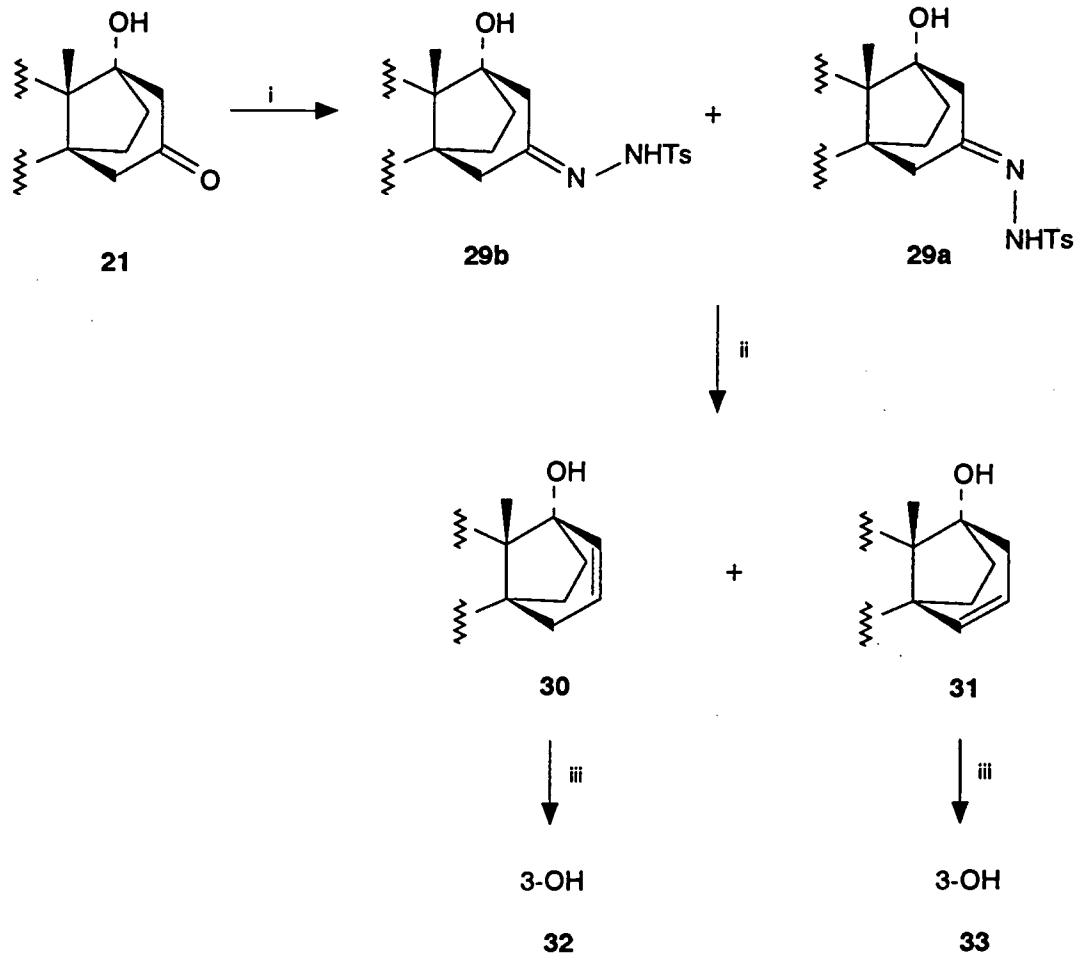
The hydroxy ketone (**21**) was treated with tosyl hydrazide and a catalytic amount of trifluoroacetic acid in tetrahydrofuran, giving rise to two separable and crystalline products (Scheme 3.13). These were only partially characterised (mass, infrared, NMR, m.p.) because of a tendency to isomerise in solution. They proved to be the two geometric isomers of the tosylhydrazone (**29**). Arenesulfonylhydrazones exist as a mixture of (*E*)- and (*Z*)-isomers which 'usually cannot be physically separated at ambient temperatures, because the inversion barrier of the azomethine bond is too low, although spectroscopic methods can distinguish between the two isomers'.[47] The *E*:*Z* ratio for a hydrazone depends on the sizes of the groups attached to the azomethine carbon, with the less sterically crowded (*E*)-isomer often predominating.[48]

In solution, the ^{1}H-NMR spectra of the chromatographically purified compounds **29a** and **29b** showed duplication of key signals (eg. tosyl group AB pattern), thereby indicating that *syn-anti* isomerisation was occurring, but it was not possible to assign the respective geometries from NMR evidence. The spectroscopic and analytical data was consistent with the proposed structure for these intermediates.

Other methods of tosylhydrazone formation were compared, including the use of *p*-TsOH as catalyst in refluxing ethanol,[49] and the use of glacial acetic acid as solvent with no added acid catalyst.[50] The results were similar for all three methods.

The Shapiro reaction involves the elimination of a tosylhydrazone with alkyllithiums.[51] The tosylhydrazone forms a C,N-dianion (**ii**) (Scheme 3.14). Facile elimination of the tosyl group and N_2 gives rise to a vinyl carbanion (**iii**), which can then be trapped by an electrophile (eg. E=H when quenched with H_2O).[52,53]

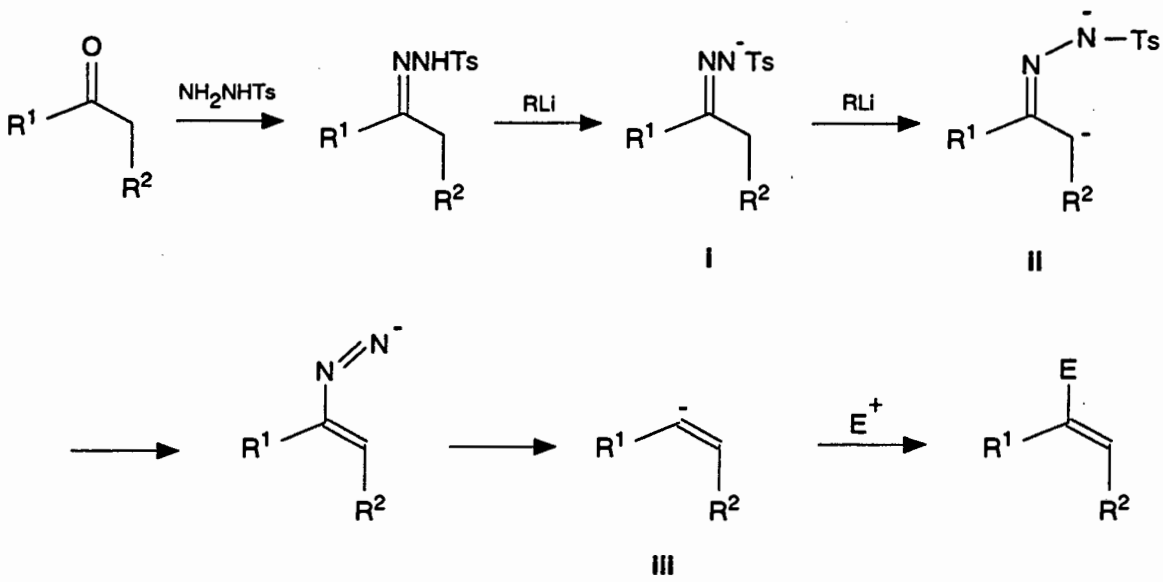
Scheme 3.13



i, NH_2NHTs; ii, n-BuLi; iii, DIBAH

With an unsymmetrical ketone, the regioselectivity of this reaction depends on the geometry of the initial tosylhydrazone, and on the solvent. The position of the double bond in the product must depend on the site of initial C-H deprotonation in the formation of (**ii**). In hydrocarbon or ether solvents, the dianion (**ii**) which is formed is exclusively *syn*. This *syn*-dianion effect results from 'the monoanion (**i**) which coordinates and directs the incoming alkyllithium to deprotonate the anion (**i**) on the same flank of the C=N bond',[52] ie. a chelation effect exerted on the alkyllithium by the tosylhydrazone monoanion (**i**).[53] Thus, in these solvents, the geometry of the tosylhydrazone controls the regioselectivity of olefin formation.

Scheme 3.14



Treatment of a mixture of the isomers (**29a** and **29b**) with an excess of n-butyllithium in tetrahydrofuran at 0°C, and quenching with water (ie. Electrophile=H), gave rise to two separable and crystalline products (Scheme 3.13). These were identified as the desired olefinic alcohols (**30**) and (**31**), but the regiochemistry was not unambiguously assignable from the spectrometric data available. Alkyllithium treatment of **29a** gave rise to **31**, and **29b** to **30**, consistent with the *syn*-dianion effect. Salient features of the ^{1}H- and ^{13}C-NMR spectra of **30** and **31** are tabulated for clarity (Table 3.15)

The further splitting of the 17^{1}-signal of **30** is probably due to a four-bond coupling to one of the 16-protons (J 2.3 Hz) and to an allylic coupling with one of the 17^{3}-protons (J 1.5 Hz). Similarly, 17^{3}-H of isomer (**31**) exhibited allylic and W-couplings to 17^{1}- and 15-H respectively.

The chemical shift differences for C(17^{1}) and C(17^{3}) for isomers (**30**) and (**31**) respectively suggest that C(17^{1}) in **30** experiences the deshielding effect of the 17-OH. Likewise, the 17^{1}-olefinic bond exerts an anisotropic effect on C(17), which experiences a downfield shift in **30**. C(17^{1}) in **31** also exhibited the deshielding effect of the 17-OH in comparison with C(17^{3}) of **30**. These features confirm the proposed structures of the olefinic alcohols (**30**) and (**31**); furthermore, this regiochemical assignment was supported by independant chemical correlation to be discussed later.

Table 3.15: Table of NMR features of olefinic alcohols (**30**) and (**31**)

Proton	**17^1-olefin (30)**	**17^2-olefin (31)**
17^1-H	δ 5.75 (ddd, *J* 9.8, 2.3 and 1.5 Hz)	not identified
17^2-H	δ 5.5 (ddd, *J* 9.8, 3.9 and 2.6 Hz)	δ 5.51 (ddd, *J* 9.6, 3.8 and 2.7 Hz)
17^3-H	δ 2.18 (ddd, *J* 17.8, 3.9 and 1.5 Hz)	δ 5.88 (ddd, *J* 9.6, 2.2 and 2 Hz)
Carbon		
C(17)	δ 82.3 (s)	δ 81.7 (s)
C(17^1)	δ 136.9 (d)	δ 42.5 (t)
C(17^2)	δ 123.8 (d)	δ 123.6 (d)
C(17^3)	δ 38.6 (t)	δ 135.6 (d)
C(18)	δ 14.0 (q)	δ 13.2 (q)

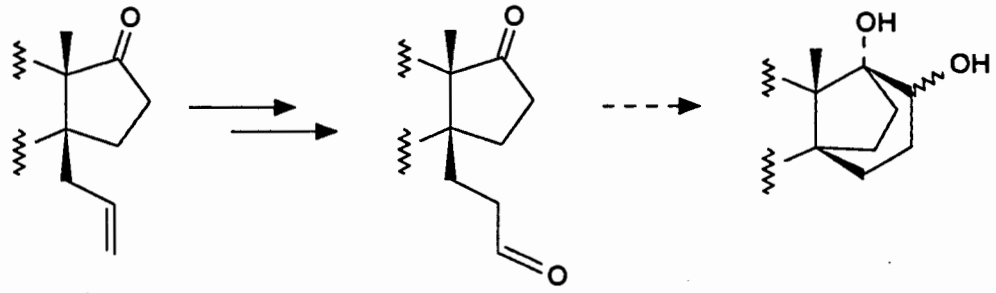
Both unsaturated isomers (**30** and **31**) were deprotected at the 3-position in the conventional manner (DIBAH in refluxing toluene), giving rise to the estradiol analogues (**32** and **33** respectively), which were submitted for receptor-site affinity evaluation.

3.4 Terminal Functionalisation of 14-Allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (18)

In order to synthesise the 17^1-hydroxylated 14,17β-propano bridged analogues of estradiol, we envisaged a regioselective oxidation of the 14β-allyl group of the allyl ketone (**18**), leading to a 14β-formylethyl 17-ketone, upon which reductive coupling of the two carbonyl groups was then expected to give the target molecules. This reductive coupling concept has been used successfully with the 14β-formylmethyl 17-ketone.[27]

The obvious approach to the regioselective oxidation was via hydroboration-oxidation of the side-chain olefinic bond of **18**, followed by oxidation of the primary alcohol to the corresponding aldehyde (Scheme 3.16).

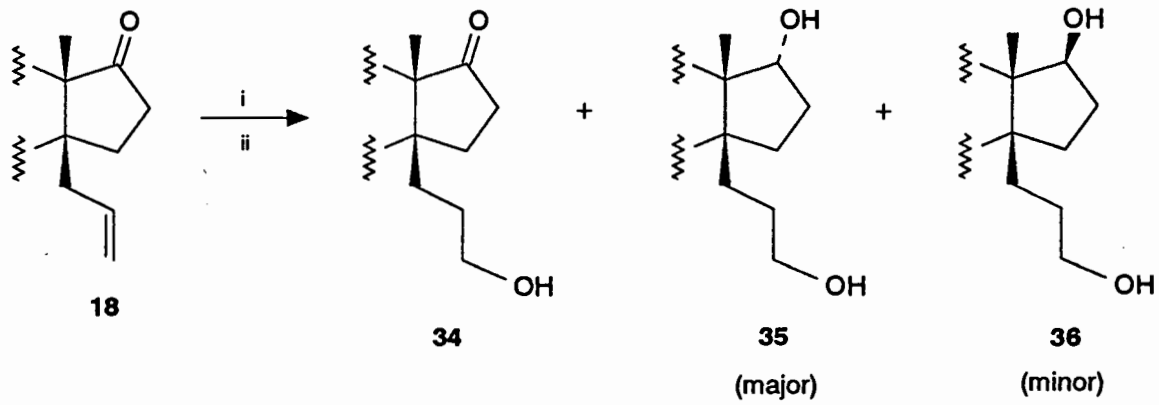
Scheme 3.16



18

Hydroboration-Oxidation. Treatment of the allyl ketone (**18**) with the relatively thermally-stable borane-dimethyl sulfide complex ($BH_3.SMe_2$) as the hydroborating agent,[54] in refluxing tetrahydrofuran for 2 h, followed by standard alkaline peroxide work-up, gave good yields (90%) of the diols (**35** and **36**) as an inseparable mixture, along with a minor amount (2%) of the hydroxy ketone (**34**) (Scheme 3.17).

Scheme 3.17



18 **34** **35** (major) **36** (minor)

i, $BH_3.SMe_2$; ii, HOO^-

Repeated recrystallisations of the diol mixture isolated the major isomer (**35**) with 17α-OH, which was fully characterised. The 14^3-protons of diol (**35**) resonated as a two-proton multiplet at δ 3.58, while 17β-H was observed as a doublet of doublets (*J* 9.1 and 7 Hz) at δ 4.21 in the NMR spectrum of the compound. The stereochemistry at C(17) was assigned on the basis of analogous 14β-functionalised 17-alcohols.[17,55] A strong OH absorption band at ν_{max} 3611 cm^{-1} in the infrared spectrum of **35**, and other analytical data was consistent with the proposed structure. In practice, however, the mixture of diols

(**35** + **36**) was used without separation in the next step. An NMR investigation of the mixture indicated a 7:2 ratio of isomers (from the relative intensities of the 13β-methyl singlet). A dd (*J* 7.8 and 3.3 Hz) at δ 3.72 was assigned to the 17α-proton of the minor diol component (**36**).

The ^{1}H-NMR spectrum of hydroxy ketone (**34**) showed the 14^3-protons as a triplet (*J* 2 x 6 Hz) at δ 3.57. Absorption bands at ν_{max} 3621 cm^{-1} (OH) and 1726 cm^{-1} (C=0) in the infrared spectrum of **34**, and a molecular ion of m/z 342 supported the proposed structure.

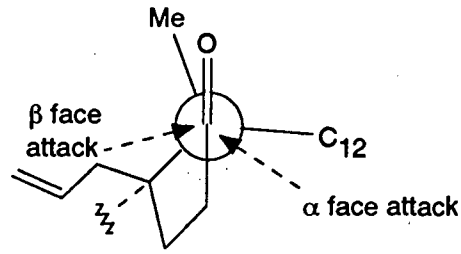
Borane-THF was also used as a hydroborating agent in an attempt to improve product recoveries at the expense of chemoselectivity. The reaction of BH_3-THF with the allyl ketone (**18**) required 90 min at 0°C. Standard alkaline peroxide conditions were employed for the oxidation. This gave the hydroxy ketone (**34**) (32%) and an inseparable mixture of diols (**35**) and (**36**) (30%).

It is well known that less hindered borane species reduce carbonyl functions.[56] The B-H species adds across the C=O, the empty orbital on boron being filled with the lone pair on oxygen. The fact that the major diol in this case was the 17α-OH epimer (**35**) appeared inconsistent with respect to expected face selectivities in hydride reduction of the 17-carbonyl group. Reduction of the ketone using other hydride sources was thus examined in order to gain further insight into the reasons behind the product distribution found with borane.

Treatment of the allyl ketone (**18**) with lithium aluminium hydride (LAH) in tetrahydrofuran at 0°C for 30 min gave rise to a separable mixture of two products, the 17β-alcohol (**37**) and the 17α-alcohol (**38**) epimers, in a 1.25:1 ratio. The stereochemistry of at the C(17) was again assigned on the basis of analogy. The 17α-proton of **37** resonated as a partially obscured doublet of doublets (*J* 8.1 and 3.2 Hz) at δ 3.73 in the ^{1}H-NMR spectrum. The corresponding signal in the derived 17β-acetate (**39**) was more clearly defined in the expected downfield region, namely at δ 4.82 (dd, *J* 8.1 and 3.2 Hz). The 17β-proton of allyl alcohol (**38**) was assigned to the signal at δ 4.22 (dd, *J* 8.8 and 7.6 Hz). The corresponding signal in the derived 17-acetate (**40**) at δ 5.18 (dd, *J* 9.1 and 6.9 Hz) was partially obscured by the 14^2-H_2 multiplet. Treatment of the allyl ketone (**18**) with lithium tri-*sec*-butyl borohydride (L-Selectride®) in tetrahydrofuran at 0°C for 2 h gave the 17β-alcohol (**37**) stereoselectively.

The crowded steric environment around C(17) of the allyl ketone (**18**) is obvious from models. In Figure 3.18, the dominant steric influences can be seen to arise from the 14β-allyl group and the C(13)-C(12) bond. The β-face is, however, slightly more hindered than the α-face towards nucleophilic attack. This similarity in steric impedence is reflected in the lack of face selectivity shown for the approach of a simple hydride (LAH). The slight weighting in favour of α–face attack is, however, amplified in the

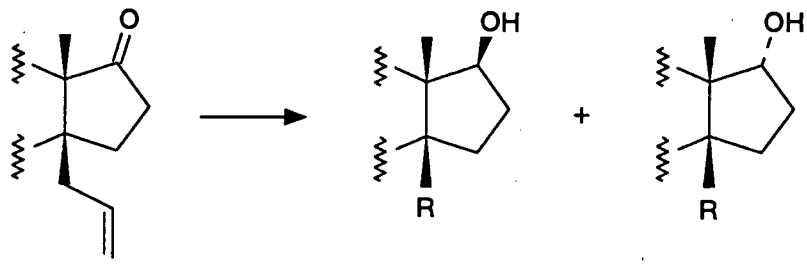
presence of a bulky hydride (L-Selectride®). When borane was employed as a reducing agent, however, a preference for β-addition of a hydride equivalent was observed (Table 3.19).



C(17) - C(13) projection

Figure 3.18: Steric factors influencing the approach of a nucleophile to the allyl ketone (**18**)

Table 3.19: Comparison of Face Selectivity on Reduction of the Allyl Ketone (**18**)



	REAGENT	RATIO		
R=Allyl	$LiAlH_4$	55	45	(isolated)
R=Allyl	L-Selectride	100	0	(from TLC)
R=Hydroxypropyl	BH_3	20	80	(from NMR)

This reversal of the hydride trend observed with LAH and L-Selectride® led us to suspect participation of the allyl group olefinic bond in directing the borane species to add across the β-face of the 17-carbonyl group (Figure 3.20). There is analogy for this type of directing influence of a remote double bond on borane addition.[57]

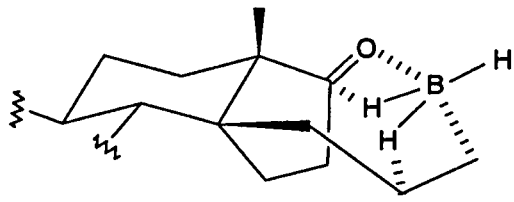
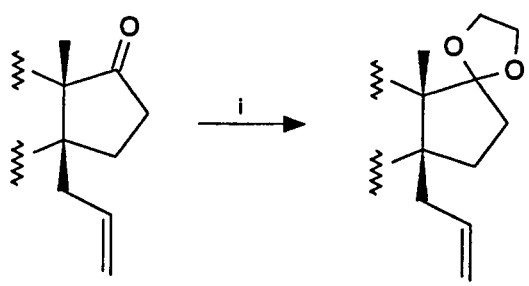


Figure 3.20: Participation of the allyl group

An attempt to circumvent the problem of isomeric mixtures arising from reduction during hydroboration was made via prior ketalisation of the allyl ketone (**18**). Conducting the reaction under conventional conditions (ethylene glycol, catalytic *p*-TsOH, benzene, Δ),[58] however, was ineffective. A variation in which toluene was slowly distilled off to concentrate the ethylene glycol gave the best yield (17%) of the desired ketal (**41**) (Scheme 3.21). Use of these forcing conditions resulted in some decomposition of the starting material over prolonged periods of reaction.

Scheme 3.21



18 **41**

i, $HO(CH_2)_2OH$, TsOH

An attempt to employ a more recently reported method involving the use of 1,2-bis(trimethylsilyloxy) ethane and trimethylsilyltriflate at low temperature (-78°C) was also ineffective.[59] It was clear that the 17-carbonyl group was too sterically hindered for ketalisation to occur.

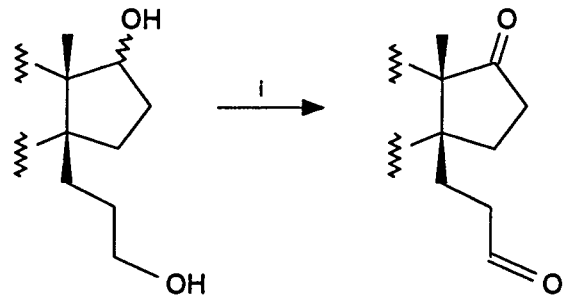
An alternative approach to chemoselective hydration of the allyl ketone (**18**) was investigated using 9-borabicyclo[3.3.1] nonane (9-BBN) in the hope that this might result in the desired functionalisation at C(14^3) without concomitant reduction of the sterically hindered 17-carbonyl group. Poor yields and lack of chemoselectivity were encountered

using 9-BBN, however. In the light of this disappointing result, further examinations of hindered borane reagents (eg. thexyl borane or disiamyl borane) were not pursued.

Oxidation. Many oxidants exist for the conversion of primary and secondary alcohols to carbonyl compounds. Activated dimethyl sulfoxide (DMSO) is a mild oxidant, capable of effecting the oxidation of alcohols of widely different structural types and complexities. This is the basis of the Swern oxidation.[60-63]

Accordingly, the diol (**35**) was treated with DMSO and oxalyl chloride in dichloromethane at -78°C for 15 min, followed by the addition of triethylamine, to give the 14β-formylethyl 17-ketone (**42**) in satisfactory yield (67%) (Scheme 3.22). An attempt to improve the yield by conducting the reaction in tetrahydrofuran, a solvent in which the diol (**35**) was more soluble, gave a comparable yield of the oxidiation product (**42**) (70%).

Scheme 3.22



35 + 36 **42**

i, DMSO, $COCl_2$, Et_3N

We were unable to crystallise, and therefore fully characterise, the formylethyl ketone (**42**). A carbonyl absorption band at ν_{max} 1726 cm^{-1} was observed in the infrared spectrum of **42**, and the formyl proton resonated at δ 9.74 as a triplet (*J* 2 x 1.2 Hz) in the ^{1}H-NMR spectrum. The vicinal couplings are relatively small, as expected with formyl protons,[64] owing to the attenuating effect of coupling through the aldehydic carbonyl group.

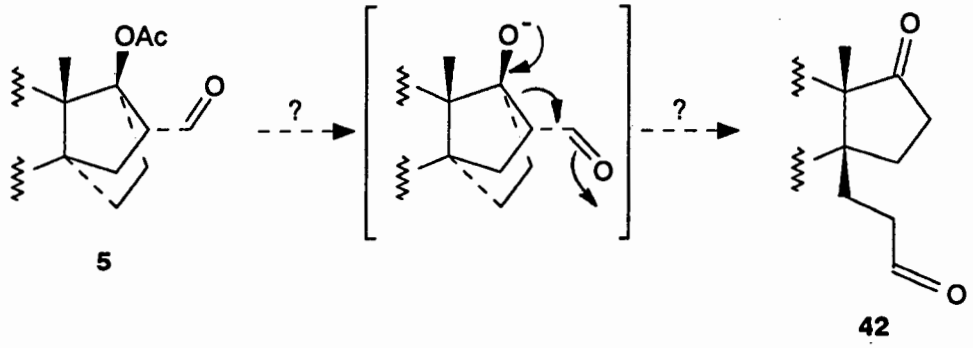
It is recognised that Swern oxidation conditions can give rise to side reactions. Therefore, an attempt was made to employ pyridinium chlorochromate (PCC) as the oxidant. PCC has been used successfully for the oxidation of steroidal primary alcohols to aldehydes.[65,66] The acidity of the reagent can be modified by the use of sodium acetate as a buffer or by adsorbing the PCC onto alumina.[67] Reaction of the diol (**35**)

with buffered PCC led to practical difficulties with respect to work-up of the tar-like reaction mixture, and product recovery was poor (33%). Hydroxy ketone (**34**) was evident as an intermediate (TLC) in the course of the reaction, an unsurprising observation in view of the more rapid oxidation of secondary alcohols than primary alcohols. This PCC reaction was unsatisfactory, and an examination of milder and more selective oxidants may provide scope for improving this oxidation step.

In the light of the foregoing results, it was concluded that the most practical route to the desired intermediate (**42**) for intramolecular reductive cyclisation would entail unselective hydroboration of the allyl ketone (**18**) followed by Swern oxidation of the three reaction products (**34**, **35** and **36**). This approach resulted in an overall conversion of 53% from the allyl ketone (**18**).

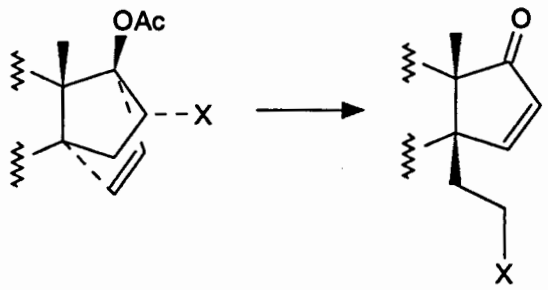
Attempted Formation of 14β-Formylethyl 17-Ketones by Retroaldol Cleavage. In an attempt to circumvent the numerous steps required to obtain the formylethyl ketone (**42**), it was decided to ascertain the outcome of a retroaldol reaction on the cycloadduct (**2**) and some of its derivatives (Scheme 3.23).

Scheme 3.23



The capricious nature of such processes is reflected in various literature reports. Thus Solo *et al.*[68] only obtained a 'complex mixture' upon treatment of 14α,17α-etheno-16α-carbomethoxyandrost-4-en-17-ol-3-one acetate with methanolic potassium hydroxide, whereas analogous cycloadducts (X=CO_2Me, SO_2Ph, CN, and COMe) have been shown to undergo clean retrograde reactions (Scheme 3.24).[19,69,70]

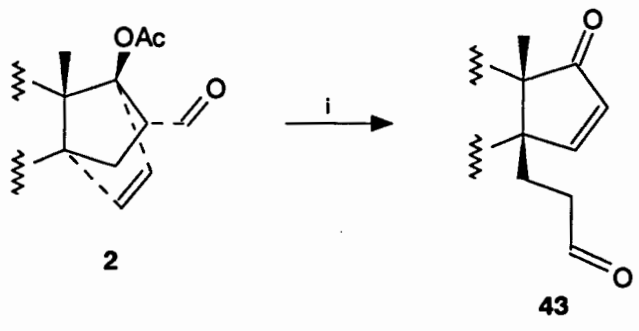
Scheme 3.24



X	Yield
CO_2Me	'complex mixture'
SO_2Ph	100%
CN	70%
COMe	90%

In the case of the acrolein cycloadduct (**2**) it was recognised that the probable lability of the product(s) arising from retroaldol reaction might militate against this becoming a synthetically useful process. Treatment of the 16α-carbaldehyde (**2**) with methanolic potassium hydroxide resulted in rapid reaction. After 2 min at 20°C, all the starting material had been consumed (TLC), and the only product that could be isolated (19%) was shown to be the 14β-formylethyl Δ^{15}-17-ketone (**43**) (Scheme 3.25). The remaining material comprised a complex mixture of polar products.

Scheme 3.25



2 **43**

i, KOH, MeOH

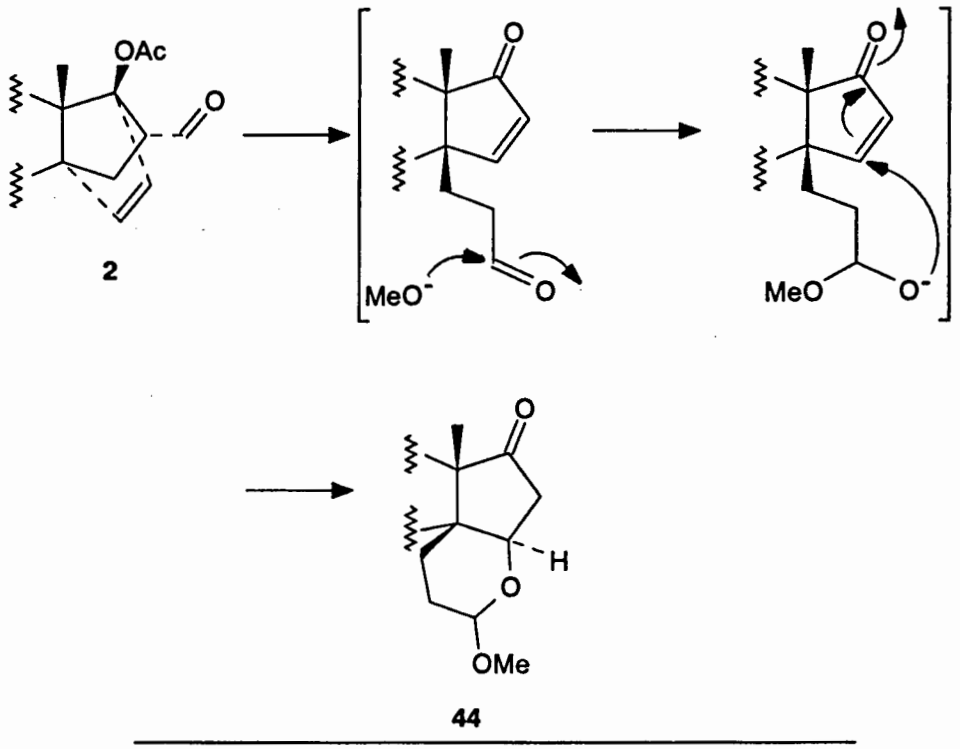
The structure of the cleavage product (**43**) was inferred from spectral properties. The ^{1}H-NMR spectrum displayed the expected AB multiplet at δ 6.22 and 7.31 (each d, *J* 6 Hz) for the 16- and 15-olefinic protons respectively. A formyl proton signal at δ 9.74

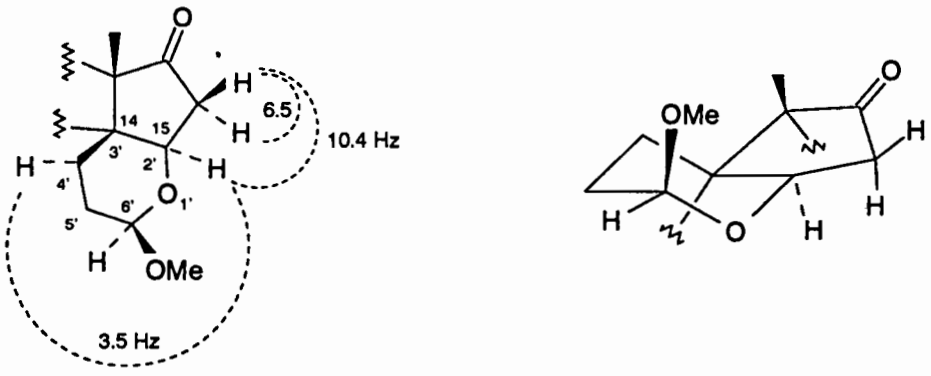
was observed as a triplet (*J* 2 x 1 Hz). The infrared spectrum of **43** showed strong carbonyl absorption bands at ν_{max} 1720 (saturated aldehyde carbonyl group) and 1700 cm^{-1} (cyclopentenone carbonyl group). The rapid reaction may be driven by formation of a conjugated enone in the product, but it is also feasible that fragmentation was incomplete after only 2 min. While only one product was isolated from the reaction mixture, the product of bridgehead hydrolysis and incomplete fragmentation may have been a component of the polar material.

By contrast, treatment of the cycloadduct (**2**) with sodium methoxide at 40°C for 30 min gave rise to a product formulated as the acetal (**44**) (40%) on the basis of spectroscopic evidence. The infrared spectrum of **44** showed a strong absorption band at ν_{max} 1723 cm^{-1} (cyclopentanone carbonyl group). The ^{1}H-NMR spectrum of **44** showed a singlet at δ 3.35 for the 6'-methoxy group of the acetal. The 15α-proton resonated at δ 4.19 as a doublet of double doublets (*J* 10.4, 6.5 and 3.5 Hz). This was due to coupling with the 16-protons, and further splitting due to long-range coupling (W-coupling) with the 4'α-H of the methyl acetal (Scheme 3.26). The 6'-proton was evident as a doublet (*J* 5.4 Hz) at δ 4.36. If the dihydropyran ring adopted a chair-like conformation, there would be further coupling to a 5'-H. This absence of splitting owing to a zero coupling implies some conformational deformation in which the ring is flattened. From models, this is achieved when the 6'-position has an *R*-configuration ie. the 6'-methoxy group is axial (6'β-OMe) with respect to the dihydropyrano ring. This is in agreement with the 'anomeric effect', which describes the finding that an alkyl group located on a carbon α to a heteroatom prefers the equatorial position, whereas a *polar* group in such a location prefers the axial position.[71] The NMR data for **44** is in agreement with similar structures, for example 3,5'ξ-dimethoxy-5'*H*,15α*H*-dihydrofurano-[3',2':14,15]-14β-estra-1,3,5(10)-trien-17-one.[72] The spectrum of this compound showed the 15α-proton at δ 4.8 (dd, *J* 9.2 and 4.5 Hz), the 5'-H at δ 5.13 (dd, *J* 6.2 and 4.3 Hz), and the 5'-OMe singlet at δ 3.35. The formation of **44** can be explained by an initial cleavage, followed by hemi-acetal formation at the 14^3-position, and Michael addition to the enone system (Scheme 3.26).

The poor results obtained from retroaldol cleavage of the cycloadduct (**2**) suggested that the initial fragmentation product was undergoing further reactions. Similar cleavage efforts were thus directed towards the dihydro compound (**5**). This substrate would prohibit further Michael addition of an intermediate hemi-acetal, and it was hoped that the major product formed would be the 14β-formylethyl 17-ketone (**42**). Treatment of **5** with methanolic potassium hydroxide for 3 h at 50°C gave three products, the formylethyl ketone (**42**) (19%), and a partially separable mixture (59%, *ca* 1:3) of two compounds, formulated as the isomeric hydroxy ketones (**45** and **46**) from spectroscopic evidence (Scheme 3.27a). The infrared spectra of both **45** and **46** showed tertiary OH (ν_{max} 3599 and 3554 cm^{-1} respectively) and carbonyl absorption bands (ν_{max} 1719

Scheme 3.26





cm^{-1}). The ^{1}H-NMR spectrum of **45** showed a dt (J 5.3 and 2 x 2.7 Hz) at δ 4.09 assigned to 16^1-H_R, and the 16α-proton resonated at δ 2.72 (t, J 2 x 5.3 Hz). The spectrum of **46** was similar, the signal arising from 16^1-H_S resonating at δ 3.82 (ddd, J 10.7, 6.3 and 3.9 Hz), and that for 16α-H at δ 2.64 (dd, J 6.3 and 3.7 Hz).

Assuming that the bicyclo[3.2.1] octanoid skeleton has the six-membered ring in a chair conformation, then with an *R*-configuration at C(16^1), the methoxy group would be axially oriented (Scheme 3.27b). The equatorial 16^1-H then has three synclinal interactions with vicinal protons. This configuration accounts for the smaller couplings

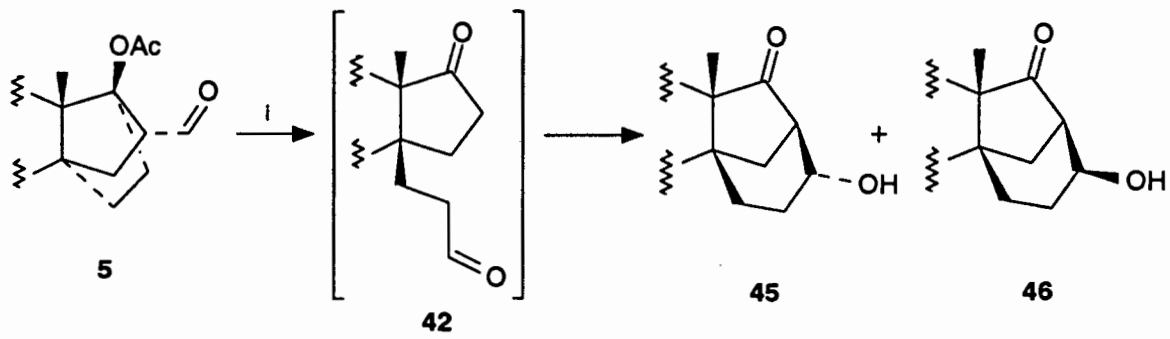
found for hydroxy ketone (**45**). An *S*-configuration at C(16^1), with an axial 16^1-proton, would create one antiperiplanar and two synclinal interactions with neighbouring protons. This is consistent with the large and two smaller couplings found in the NMR spectrum of hydroxy ketone (**46**). This stereochemical assignment would, however, be reversed if the new six-membered ring adopted a boat-like conformation, which could be possible in view of the *endo*-disposition of the sterically-demanding 13β-methyl group. Allinger,[73] however, calculated the preference of the cyclohexane ring of bicyclo[3.2.1] octane systems to adopt a chair conformation as *ca* 27 k.J.mol^{-1}. This is a sufficiently large energy barrier to generate confidence in the above argument. Additionally, if the reaction proceeds via the formylethyl ketone (**42**) as an intermediate, a transition state in which the 14β-side chain lies over the β-face of ring D can be envisaged. The unlike faces of the 14^3-carbonyl group and the C(16) sp^2 centre would be presented to one another for optimal carbonyl dipole line-up, giving rise to a chair-like six-membered transition state. This would result in a major isomer with *S*-configuration at C(16^1) (Figure 3.27c). This is in agreement with the results obtained, in which the couplings are consistent with 16^1-H_S for the major isomer (**46**).

The formation of hydroxy ketones (**45**) and (**46**) can be explained by initial retroaldol cleavage, followed by enolisation of the 17-ketone in the presence of the base, and intramolecular aldol condensation with the 14^3-carbonyl group. This reaction was not optimised, since the 14,16-bridged products were not useful for this project and there was a lack of selectivity in the closure.

The dimethyl acetal (**4**) also seemed a possible candidate for direct or indirect fragmentation. Treatment of **4** with methanolic potassium hydroxide, however, mainly gave rise to hydrolysis of the bridgehead acetoxy group, an unsurprising result (Scheme 3.28). The 16β-proton resonated at δ 2.42 as an obscured triplet of doublets (*J* 8.9 and 2 x 3.9 Hz), and 16^1-H was assigned to the signal at δ 4.18 (d, *J* 8.9 Hz) in the NMR spectrum of the 17β-hydroxy 16^1-dimethyl acetal (**47**). This hydrolysis could be carried out more efficiently using lithium aluminium hydride. It may be of interest to determine the outcome of subjecting the product (**47**) to conditions for indirect retroaldol fragmentation.

Scheme 3.27

a:



5 42 45 46

i, KOH, MeOH

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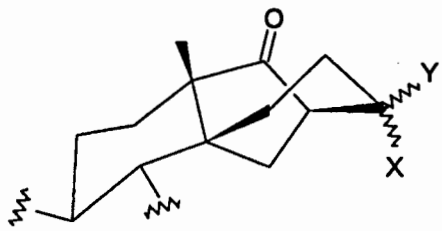
b:



X=OMe, Y=H

X=H, Y=OMe

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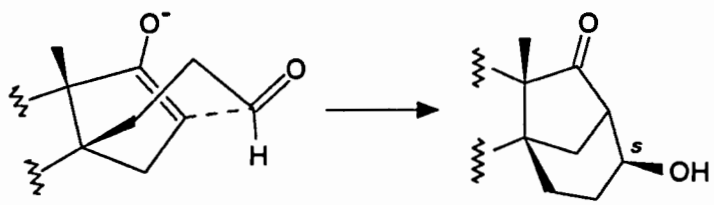
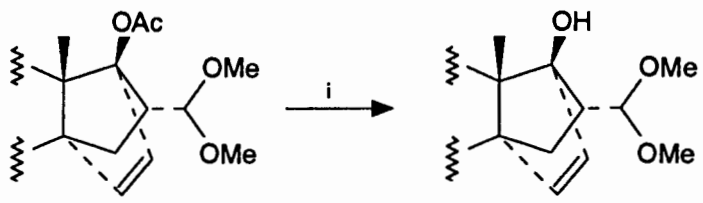
c:



46

Scheme 3.28



4 47

i, KOH, MeOH or LAH, THF

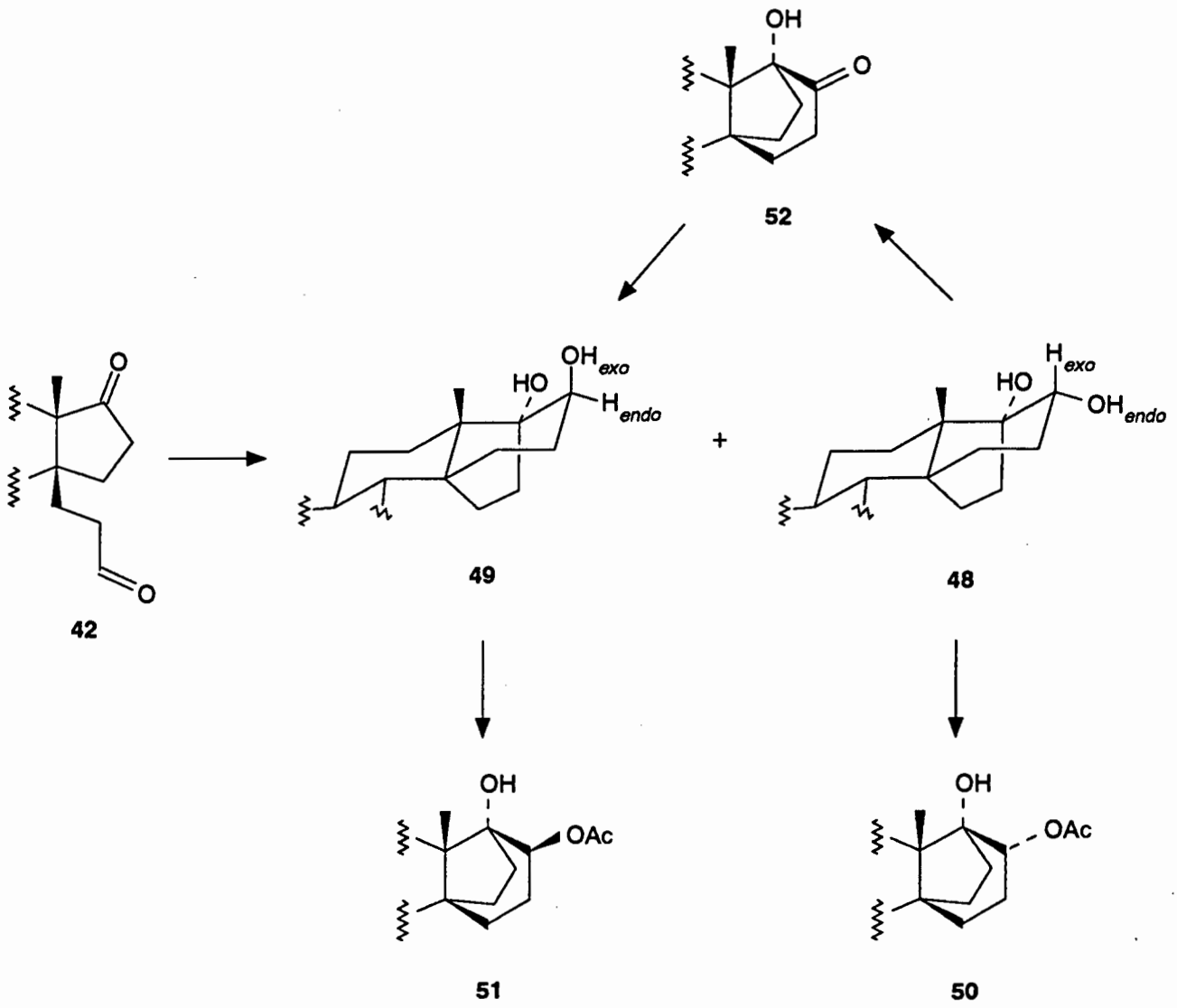
In summary, it is evident that further work on the retroaldol cleavage of the dihydro cycloadduct (**5**) offers the promise of an efficient route to the 14β-formylethyl 17-ketone (**42**), provided that reaction conditions can be developed to trap the desired product or to inhibit further intramolecular reactions.

3.5 Intramolecular Reductive Coupling of 3-Methoxy-14-formylethyl-14β-estra-1,3,5(10)-trien-17-one (42)

For the purposes of this investigation, the hydroboration-oxidation sequence on the allyl ketone (**18**) served the purpose of providing the necessary substrate for examining intramolecular reductive cyclisation to the 14β,17β-propano system. This approach is complementary to the intramolecular aldol condensation route already described since the resultant 17,17[1]-diols represent additional spatial analogues of 'estriol', which were expected to provide further insights into structure-activity relationships in the 14β,17β-propano bridged series.

The reportedly 'optimised procedure' of McMurry,[74] involving a titanium(III) chloride-dimethoxyethane complex [nominally $TiCl_3(DME)_{1.5}$] in conjunction with a zinc-copper couple to generate a low-valent titanium species was used for the reaction. The titanium reagent was generated by refluxing titanium(III) chloride with 1,2-dimethoxyethane (DME) for two days. This source of titanium is described by McMurry as allowing for reproducibility and higher yields of carbonyl coupling reactions. Large volumes of DME as solvent were used to avoid or minimise intermolecular couplings,[75] although this was not expected to be a problem in view of the apparently hindered nature of the 17-oxo group (*cf* attempted ketalisation). Low temperatures are usually used in the coupling process, in order to avoid reductive elimination of the resultant glycols.[75,76] In this case, however, the formation of a bridgehead hydroxy group would exclude this problem. Accordingly, the formylethyl ketone (**42**) was treated with the McMurry reagent in DME at 20°C. After 3h, starting material was no longer present (TLC), and direct recrystallisation of the polar reaction mixture gave the major product (**48**) (50%). Chromatography of the mother liquor residue gave a minor product (**49**) (*ca* 4%) and further **48** (3%) (Scheme 3.29).

Scheme 3.29



The two products (**48**) and (**49**) were identified as the epimeric 17,17[1]-diols. The limited solubility and polarity of these products rendered chromatography and complete characterisation difficult, so that their respective monoacetates (**50**) and (**51**) were prepared (acetic anhydride, pyridine) and fully characterised. Table 3.30 summarises the ^{1}H-NMR data pertaining to the 17[1]-H of the diols (**48**) and (**49**) and their derivatives (**50** and **51**).

Table 3.30: Summary of NMR Data for the 17^1-protons of Diols (**48**) and (**49**) and the Derived Acetates (**50**) and (**51**)

Compound	δ (ppm)	Mult., *J* (*W*)/Hz	Assignment
48	3.99	t, 2 x 8 (16)	17^1-H_x
49	3.84	d, 6.2 (6.2)	17^1-H_n
50	5.32	ddd, 9.8, 6.8 and 1.8 (18.4)	17^1-H_x
51	4.9	d, 5.5 (5.5)	17^1-H_n

These data are consistent with the assignment of (17^1R)-configuration to the major diol (**48**) and (17^1S)-configuration to the minor diol (**49**). The signal width of 17^1-H_x (ie. *exo* with respect to the bicylic ring D system) in the derived acetate (**50**) (18.4 Hz) accomodates an axial orientation, and the coupling magnitude and multiplicity are appropriate for antiperiplanar and synclinal neighbours, along with a four-bond coupling (*J* 1.8 Hz) to 15α-H. In the case of the minor isomer (**49**), the doublet (*J* 5.5 Hz) for 17^1-H_n (ie. *endo*-disposed) supports an equatorial orientation and suggests further that a degree of conformational deformation may be present to account for the absence of coupling with one of the neighbouring protons. This may be rationalised in terms of the resultant relief of steric strain arising from the 1,3-diaxial interaction between the 17^1-hydroxy and 13β-methyl groups (Figure 3.31). The relative chemical shifts of the signals for 13β-Me also support the assignments, since that of the minor isomer (**49**) displays a significant downfield shift in response to the 1,3-diaxial interaction (δ 1.13 for **49**, *vs* δ 0.88 for **48**).

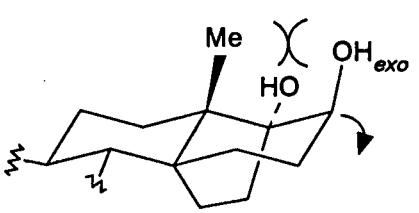
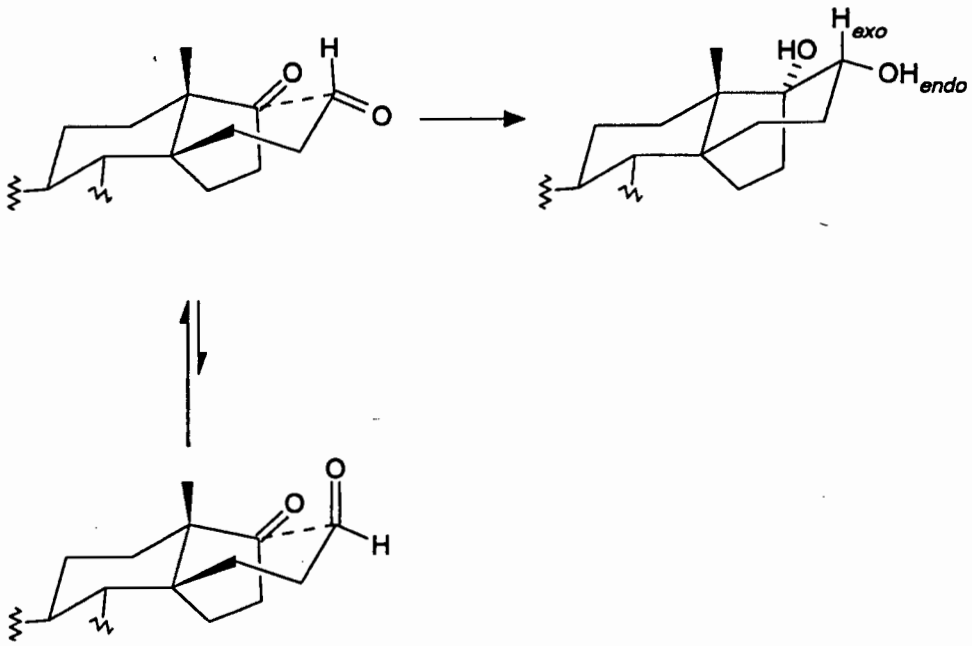


Figure 3.31: Conformational deformation in the diol (**49**)

The foregoing data are self-consistent and also exclude the possibility that the 14β,17β-propano bridge could adopt a boat-like conformation, in which case the configurational assignments would be reversed (*cf* Allinger[73]).

The stereochemical outcome of the reductive coupling is readily rationalised in terms of a bond-forming approach in which the sterically-favoured orientation of the 14^3-oxo group presents the *si*-face to the 17β-oxo moiety. The less-favoured orientation is accompanied by a sterically unfavourable interaction between the 14^3-oxo and 13β-methyl groups (Scheme 3.32)

Scheme 3.32



In order to synthesise sufficient of the minor diol (**49**) for structure-activity studies, it was necessary to use an oxidation-reduction sequence, since an attempt to carry out an inversion at C(17^1) of the major diol (**48**) under Mitsunobu conditions[77] was unsuccessful. The major diol (**48**) was thus oxidised under Swern conditions to give the hydroxy ketone (**52**) in moderate yield (63%) (Scheme 3.29).

The infrared spectrum of the hydroxy ketone (**52**) showed the appropriate absorption bands at ν_{max} 3480 and 1706 cm^{-1} for the 17-hydroxy and 17^1-oxo groups respectively. In the ^{1}H-NMR spectrum, signals for the protons α to the carbonyl group were found at at δ 2.48 (ddd, *J* 17.1, 7.7 and 1.4 Hz, 17^2-H_{proS}) and δ 2.56 (m, *W* 38 Hz, 17^2-H_{proR}). Use of benzene-d_6 as solvent for the spectrum separated the 17^2-proton signals better, but the higher-field 17^2-H_{proS} was then obscured by another signal. The 17^2-H signals simplified on D_2O exchange, implying five-bond coupling to the 17-OH, which resonated as a singlet at δ 3.69, and was D_2O exchangeable. From models, the 17^2(pro*S*)-proton has an orthogonal relationship with 17^3-H_{proS}. This factor would account for the large vicinal coupling to 17^3-H_{proR}.

The hydroxy ketone (**52**) was subjected to lithium aluminium hydride reduction in tetrahydrofuran, the reaction taking 30 min at 0°C (Scheme 3.29), to give the diol (**49**) as the major product, accompanied by a trace amount of the epimeric compound (**48**) (TLC - not isolated). The stereoselectivity of the reaction was as expected, and arose from *endo*-attack by the hydride, since *exo*-approach would be strongly impeded by a 1,3-diaxial interaction with the 13β-methyl group.

Both diols, (**48**) and (**49**), were subjected to demethylation conditions (*viz.* DIBAH in refluxing toluene, 24h) to yield the 3,17,17^1-'estriol' analogues (**53**) and (**54**) which were submitted for biological evaluation. The products were extremely insoluble, enabling only mass spectra and microanalyses to be recorded. These data were consistent with the proposed structures.

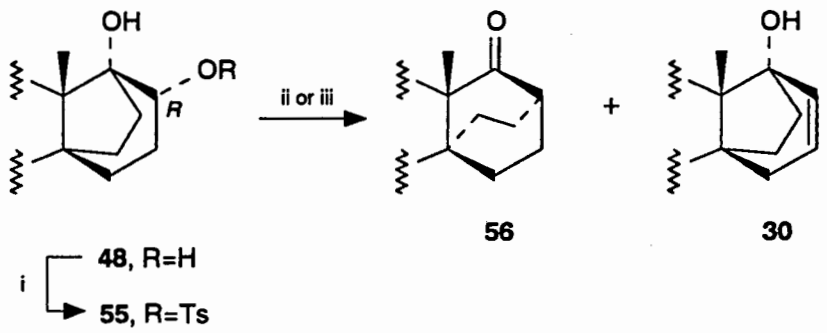
3.6 Formation and Attempted Elimination of the 17^1- and 17^2-Tosylates of the 14β,17β-Propano 17α,17^2*S*-Diol (26) and the 14β,17β-Propano 17α,17^1*R*-Diol (48)

During the investigation directed towards the synthesis of 14β,17β-propano analogues of estradiol *via* Shapiro elimination of the 17^2-tosylhydrazone (**29**) (*cf.* section 3.3), the lack of regioselectivity during the elimination step detracted from the synthetic efficiency of the reaction sequence. Furthermore, the structural assignments of the regioisomeric olefins (**30**) and (**31**), although supported by spectroscopic data, were not conclusively proved. Accordingly, it was decided to attempt a regiodefined synthesis of the 14β,17β-prop-17^1-eno compound (**30**) *via* elimination of the 17^1-hydroxy group in the 17α,17^1-diol (**48**) in order to confirm the assignments.

Treatment of the diol (**48**) with tosyl chloride in pyridine at 7°C for 6 days yielded the 17-hydroxy 17^1-tosylate (**55**) (Scheme 3.33). The NMR spectrum of **55** confirmed the expected structure, with 17^1-H$_x$ resonating at δ 4.8 as a ddd (*J* 9.8, 7.1 and 1.5 Hz).

Treatment of the 17^1-tosylate (**55**) with basic alumina gave a single product in high yield (98%), which was formulated as the 17a-homo 14α,17α-ethano 17a-ketone (**56**). The infrared spectrum of **56** showed a strong carbonyl absorption at ν_{max} 1705 cm^{-1} (cyclohexanone C=O). The 17β-proton resonated at δ 2.54 as a multiplet (dddd, *J* 18.5, 14.1, 9.9 and 1.2 Hz) in the ^{1}H-NMR spectrum. The absence of olefinic protons, along with analogy[78] for this type of rearrangement, confirmed the proposed structure.

Scheme 3.33

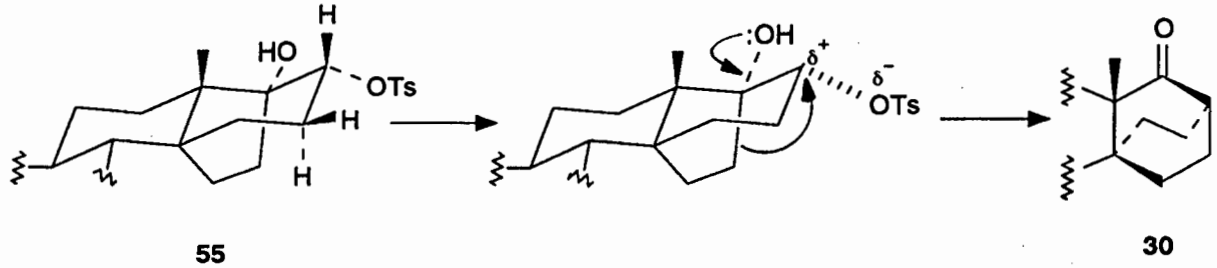


i, TsCl, pyridine; ii, DBU; iii, Al_2O_3

An attempt to conduct the elimination of the hydroxy tosylate (**55**) with 1,8-diazabicyclo[5.3.0]undec-7-ene (DBU) in refluxing toluene for 10 h, gave two products, one in trace quantities. The less polar, and major, compound was found to be 17a-homo ketone (**56**), while the minor component was identified as the desired 17^1-olefin (**30**) by TLC comparison with authentic material, thereby confirming the regiochemical assignment of the olefins (**30**) and (**31**).

With hindsight, this rearrangement product (**56**) was not surprising, since the equatorial orientation of the 17^1-tosyloxy group is poor for facile *trans*-elimination, whereas the juxtaposition of functionality for the competing 16(17→17^1)*abeo* rearrangement leading to the 17a-homo compound (**56**) is highly favourable (Scheme 3.34). Scarcity of material precluded similar treatment of the axial 17,17^1-diol (**49**), in which elimination should have been more competitive.

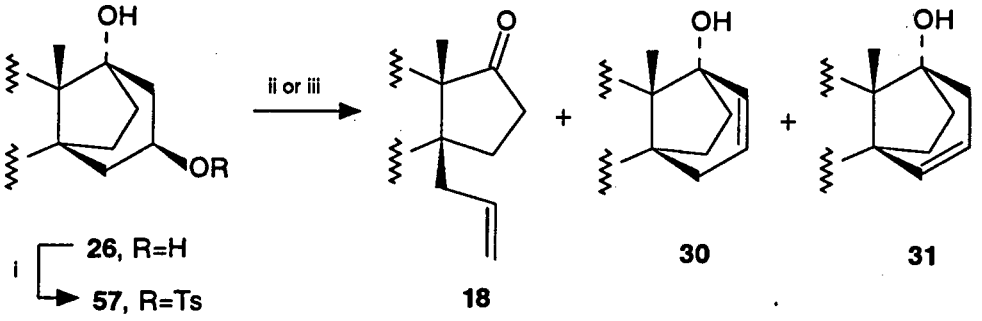
Scheme 3.34



In view of the foregoing result, it was of interest to compare the scope for applying tosylation-elimination methodology to the 17,17^2-diols, since it was recognised that here too a competing process, *viz.* Wharton fragmentation, was also possible. The

diol (**26**) was thus tosylated (TsCl, pyridine, 7°C, 24 h) in 78% yield. The 17^2-proton signal in the NMR spectrum of the hydroxy tosylate (**57**) resonated at δ 4.74 (tt, *J* 2 x 10.3 and 7.4 Hz) (Scheme.3.35).

Scheme 3.35



i, TsCl, pyridine; ii, DBU; iii, Al_2O_3

Treatment of the hydroxy tosylate (**57**) with basic alumina gave rise to the allyl ketone (**18**) as the major product (77%) formed by Wharton fragmentation of the 1,3-diol derivative, along with a trace amount of the 17^1-olefinic (**30**). A mixture of three products was formed on DBU treatment, the allyl ketone (**18**) mainly, followed by trace amounts of the olefinic alcohols (**30**) and (**31**) (TLC).

3.7 Conclusions

The overall objectives of this phase of the investigation were to use regioselective functionalisation of the 14β-allyl 17-ketone (**18**), followed by intramolecular coupling to generate the 14β,17β-propano skeleton. This strategy has been shown to succeed, and has provided access to the parent estradiol analogues, together with a series of functional variants.

Although the methods and intermediates described here provide scope for further synthetic refinement and access to additional functional variants in this series, the consistent pattern of very low binding affinities (*cf.* Chapter 6) associated with these analogues of estradiol discouraged further work.

Chapter 4

SYNTHESIS OF CYCLOPENTA[14,15] ESTRATRIENES

4.1 General Objectives

An extension of the investigations into stucture-activity relationships of 14β,17β-propano 19-norsteroids involved the introduction of unsaturation into the α-face bridge of the propanoestradiol analogue. Based on precedent,[16] in which 14α,17α-ethenoestradiol displayed enhanced binding affinities towards the estradiol receptor, the Δ^{15}-compound was identified as an important target for biological evaluation (Figure 4.1).

58 **59**

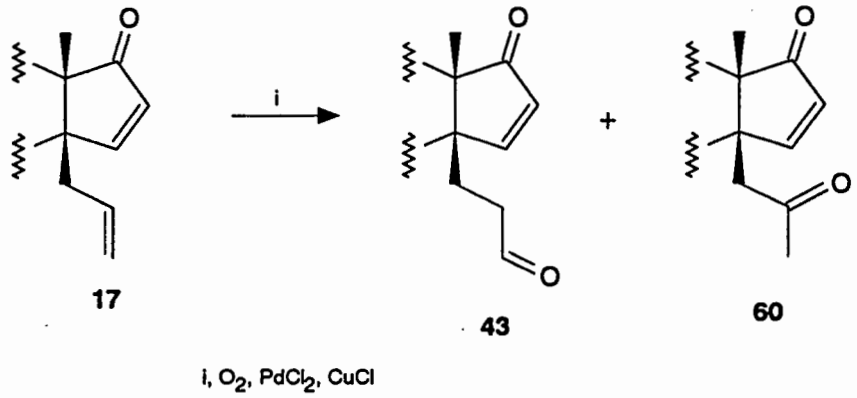
Figure 4.1: Active bridged estradiol analogues

The most obvious route to the target Δ^{15}-estradiol involved the use of a substrate containing the required unsaturation, *viz.* the 14β-allyl Δ^{15}-17-ketone (**17**) from the cycloaddition-fragmentation procedure, and mimicking of the methodology exploited in the preceding chapter. Thus, regioselective functionalisation of the 14β-allyl group, followed by intramolecular coupling with C(17) would provide access to the 14β,17β-propano Δ^{15}-estradiol. It was, however, anticipated that the regioselectivity of intramolecular closure of the functionalised enone would prove less simple than with the saturated analogues in view of the enhanced electrophilicity of C(15).

4.2 Oxidation of the Allyl Group of 14-Allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (17)

Wacker oxidation of the allyl enone (**17**) was expected to give rise to the 14β-acetonyl derivative. However, treatment of the enone (**17**) with the $PdCl_2$-CuCl catalyst system in DMF-H_2O (described in chapter 3) at 65°C for 90 min, gave rise to a partially-separable mixture (1:1 ratio, from NMR) of two products in 91% overall yield. These were separated and identified as regioisomers (**43**) and (**60**), isolated in 55% and 23% yield respectively (Scheme 4.2).

Scheme 4.2

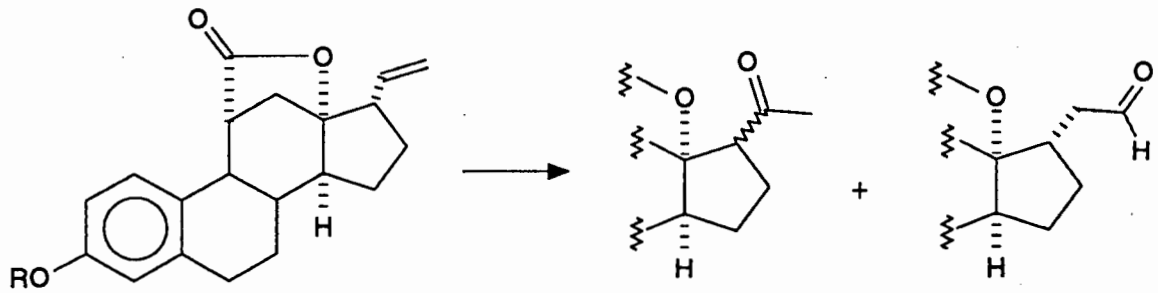


The formylethyl enone (**43**) was readily identified by spectroscopic comparison with the product derived from retroaldol cleavage of the cycloadduct (**2**) (*cf.* chapter 3), and the structure of the 14β-acetonyl enone (**60**) was evident from spectral data. Thus, in addition to the familiar features of the 14β-acetonyl group, the NMR spectrum exhibited the expected 16- and 15-olefinic proton AB multiplet at δ 6.22 and 7.39 (each d, *J* 5.9 Hz). The infrared spectrum displayed only one broad carbonyl absorption band at ν_{max} 1725 cm^{-1}.

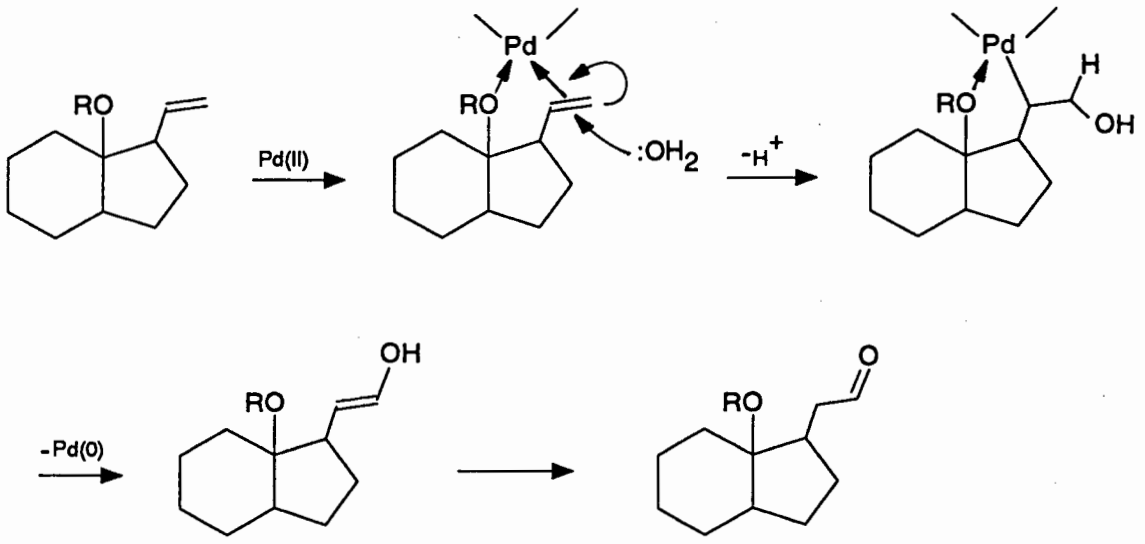
The overall conversion yield was high, but chromatographic separation of the two components was troublesome, with *ca* 15% of the material constituting mixed fractions. It was not possible to recycle the impure material for further product isolation, since the formylethyl enone (**43**) was found to be unstable, forming an unidentified decomposition product of almost identical R_f in the space of a few hours. This similarity in polarity of the regioisomeric compounds (**43**) and (**60**) did pose a problem, however, when chromatographically 'clean' 14β-formylethyl enone (**43**) was subjected to further reaction, and it became apparent that the acetonyl enone (**60**) was present as a minor impurity.

The lack of regioselectivity of the Wacker oxidation in this case was surprising. Pelissier and co-workers,[79] however, found a similar lack of selectivity when attempting the Wacker oxidation on a variety of 17α-vinyl-estra-1,3,5(10)-triene derivatives bearing 11-alkyl,13-oxo substituents on the α-face. Their findings are exemplified in Scheme 4.3. A general mechanistic interpretation for the anomalous reaction was suggested in which the 13-oxo group is essential for palladium coordination, which then influences the regioselectivity of the hydration step. The heteroatom must be *syn* to the vinyl moiety, so that, on addition of the palladium species, a five-membered ring palladium complex can be formed. This can then undergo anti-Markovnikof addition of water to yield the σ-alkylpalladium complex, which β-eliminates to form the aldehyde.

Scheme 4.3



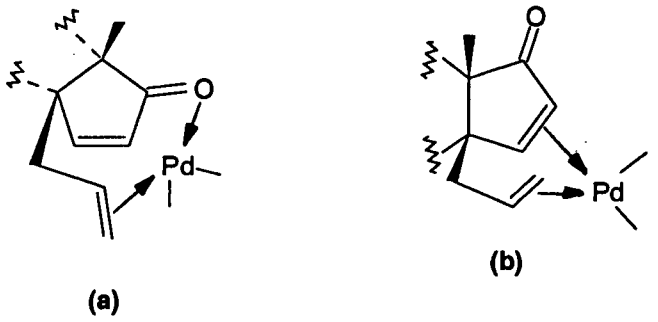
MECHANISM :



It was interesting to ascertain whether a similar postulate could be generated for the allyl enone (**17**). In this case, however, for the heteroatom to be involved, a seven-

membered ring palladium complex would need to be invoked (Figure 4.4, a). Additionally, the 17-oxo group of the analogous saturated allyl ketone (**18**) did not appear to participate in the Wacker oxidation, so that this type of Pd-O coordination in the allyl enone (**17**) would be inconsistent. Alternatively, it seems more reasonable to propose involvement of the Δ^{15}-bond in the palladium complex (Figure 4.4, b).

Figure 4.4



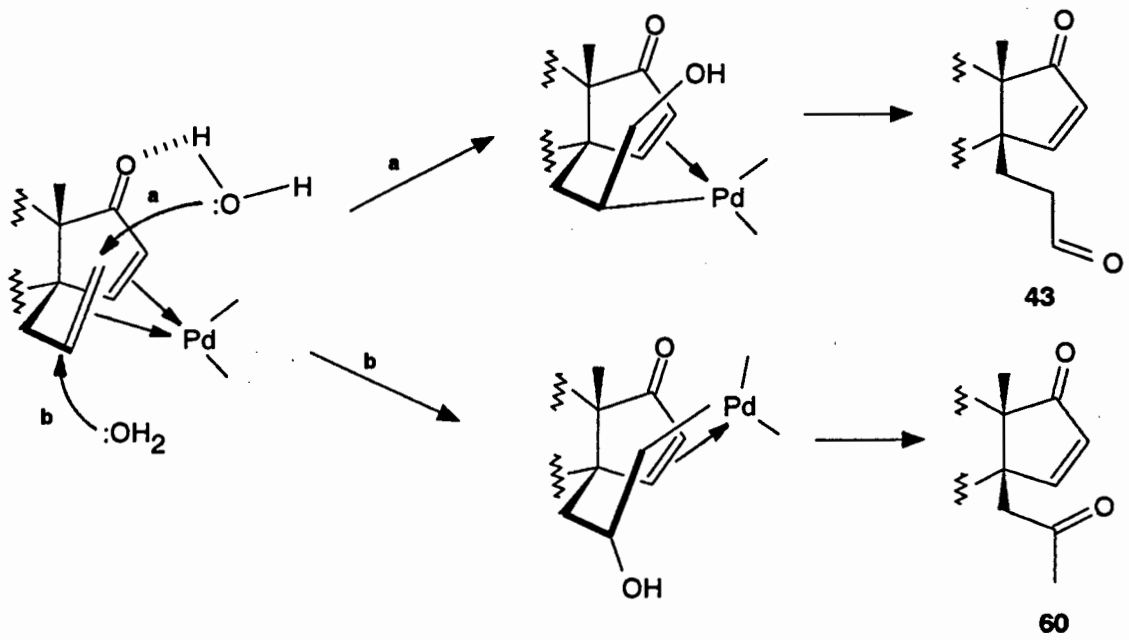
(a) (b)

From models it is clear that the 14β-allyl group can buckle over ring D in such a way that the olefinic bond is stacked above the Δ^{15}-bond. Coordination of the palladium catalyst to both double bonds is then feasible. This type of palladium complex of a 1,5-hexadienyl fragment is well-known.[80] The 17-oxo group possibly assists in directing the hydration of the complex at the 14^3-position by hydrogen bonding with the incoming nucleophile (Scheme 4.5).

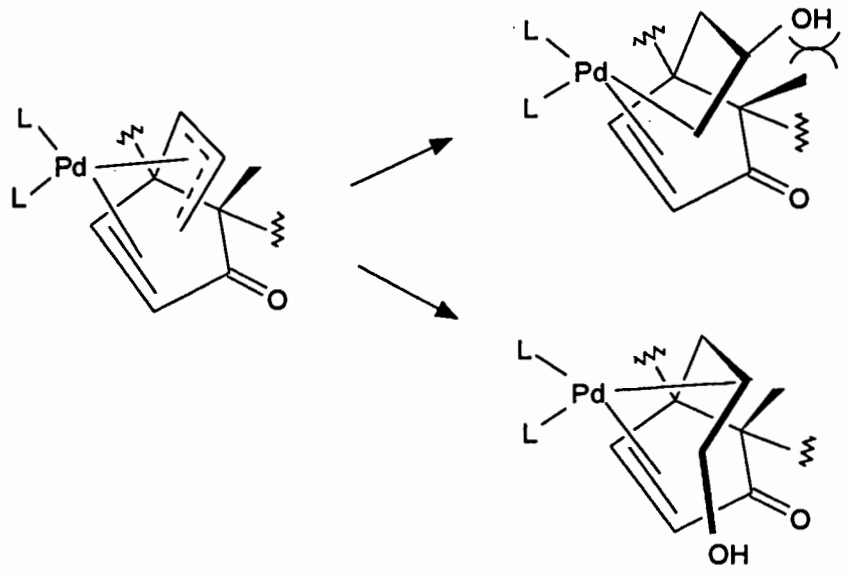
Alternatively, it is possible to envisage a similar palladium-diene complex in which a six-membered chair-like transition state forms. Competing hydration at the 14^3-position may then be sterically preferable to the unfavourable interaction with 13β-Me that 14^2-hydration would create (Scheme 4.6).

The fact that both oxo-isomers (**43** and **60**) had been generated in the Wacker step meant that there was no need to exploit the hydroboration-oxidation route to synthesise the formylethyl enone (**43**). The complementary intramolecular coupling reactions could thus be investigated, the essence of this study being the question of regiocontrol in the closure.

Scheme 4.5



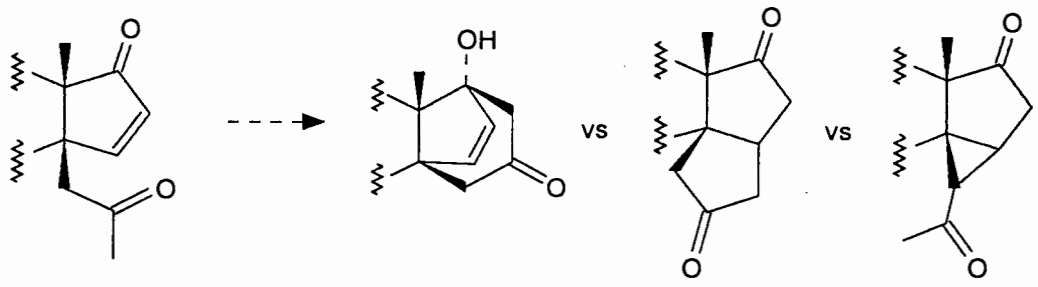
Scheme 4.6



On base treatment, the acetonyl enone (**60**) could undergo deprotonation at the terminal 14[3]-carbon followed by intramolecular Michael addition to the ring enone, to form the cyclopenta[14,15]-fused ring dione (**61**). Alternatively, an intramolecular aldol condensation analogous to that mentioned previously (chapter 3) would give rise to the

14β,17β-propano bridged compound (**59**). A further, more speculative, closure product could arise from deprotonation at C(14^1), followed by Michael addition at C(15), forming a cyclopropa[14,15] acetyl ketone (**62**) (Scheme 4.7). The ease of deprotonation at the terminal carbon of the acetonyl group, combined with the enhanced electrophilicity at C(15), was expected to facilitate formation of the diketone (**61**).

Scheme 4.7



60 **59** **61** **62**

4.3 Intramolecular Coupling of 3-Methoxy-14-acetonyl-14β-estra-1,3,5(10),15-tetraen-17-one (60)

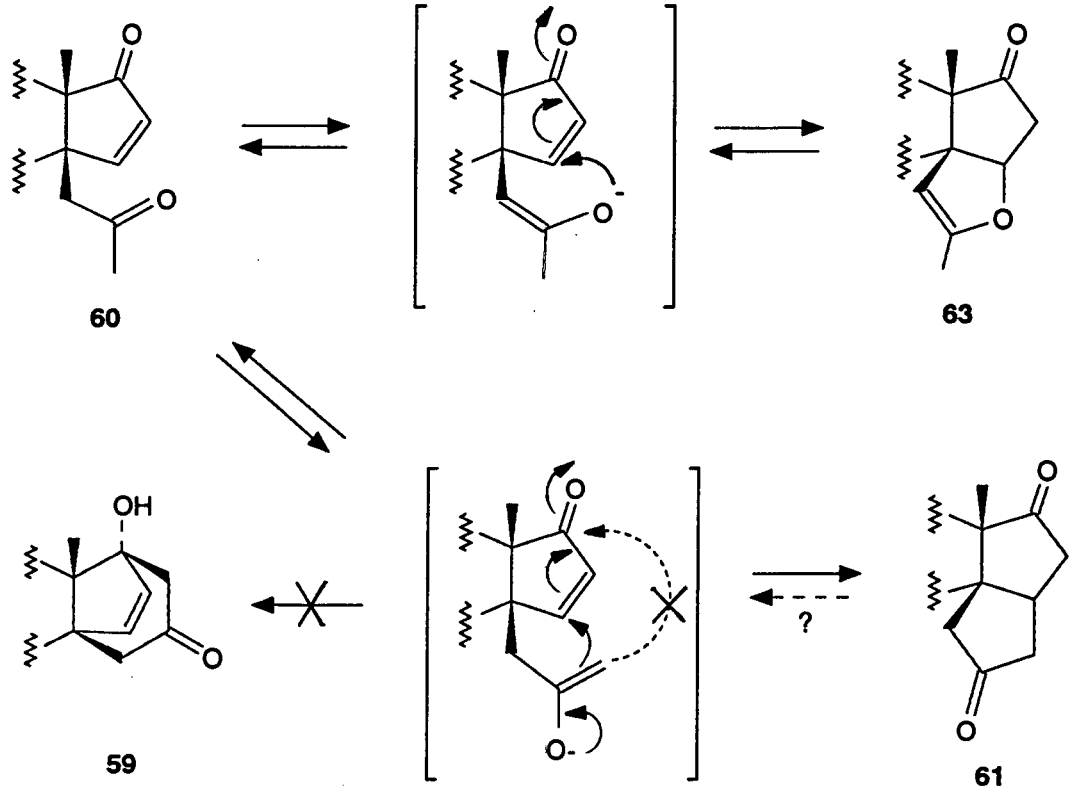
Treatment of the 14β-acetonyl enone (**60**) with methanolic potassium hydroxide at 20°C for 5 min resulted in rapid but incomplete reaction to a multicomponent mixture. If the reaction was interrupted at this stage, one of the components of the mixture could be isolated cleanly by chromatography, although in very low yield (10%). Furthermore, this product (**63**) disappeared and the mixture simplified during more prolonged reaction, so that after 2 h at 65°C, the final product (**61**) could be isolated in 64% yield (Scheme 4.8).

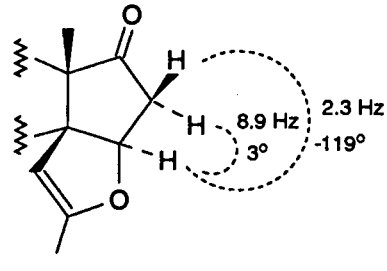
The structure of the 'intermediate' furano ketone (**63**) was inferred from well-resolved spectroscopic data. The 5'-methyl group resonated at δ 1.8 (d, *J* 1 Hz), the small splitting arising from four-bond coupling with the olefinic 4'-proton at δ 4.31 (d, *J* 1 Hz). Signals at δ 2.09 (dd, *J* 19.8 and 2.6 Hz) and δ 3.12 (dd, *J* 19.8 and 9.1 Hz) were assigned to the 16β- and 16α-protons respectively. These assignments were made on the basis of the vicinal relationship of the 16-protons with 15α-H, which resonated at δ 4.95 (dd, *J* 9.1 and 2.6 Hz).

Molecular mechanics calculations were performed on the minimised structure (*cf.* preamble to experimental for details of force field) in order to compare the calculated

dihedral angles in ring D with those found spectrometrically. Figure 4.9 shows the theoretical torsion angles and the calculated coupling constants[81] compared with the actual values found for $J_{15\alpha,16\alpha}$ and $J_{15\alpha,16\beta}$, and indicates a good correlation between the two sets of data.

Scheme 4.8





63

	J 16α-15α	J 16β-15α
Found:	9.1 Hz	2.6 Hz
Calc:	8.9 Hz	2.3 Hz

Figure 4.9: Coupling constants for compound **63**

The final product of base treatment of the acetonyl enone (**60**) was assigned the diketone structure (**61**), since analytical data were correct and the infrared spectrum displayed only a single broad carbonyl absorption band at ν_{max} 1732 cm^{-1}. The 400 MHz NMR spectrum of **61** revealed a wealth of data which were consistent with the structural assignment, but some of the detail was obscured by signal overlaps in chloroform-*d* ($CDCl_3$). Accordingly, spectra were also recorded in benzene-d_6 (C_6D_6) for comparative purposes and to clarify details of ring D signals through differential responses of the signals to solvent-induced chemical shifts. A detailed analysis of the data was justified by the novelty of the fused ring system, and the assignment of all the signals associated with the ring D and E protons was expected to facilitate interpretation of the NMR spectra of further products in this series. Assignments for the $CDCl_3$ spectrum will first be discussed. The ^{13}C, DEPT, HETCOR and long range HETCOR pulse sequences allowed a number of unambiguous assignments to be made. Of the aliphatic trisubstituted carbon resonances, it was possible to distinguish C(15) from C(8) and C(9) by exclusion. A crosspeak in the HETCOR spectrum located 15α-H as part of a two-proton multiplet at δ 3.14. Analysis of the abovementioned spectra also allowed the signals arising from C(16), C(3') and C(5') in the ^{13}C spectrum to be distinguished from the remaining disubstituted carbon resonances. The ^1H-NMR, COSY and HETCOR spectra of the high-field region are shown in Figure 4.10, and the ring D and E proton assignments have been tabulated in Table 4.11 for clarity.

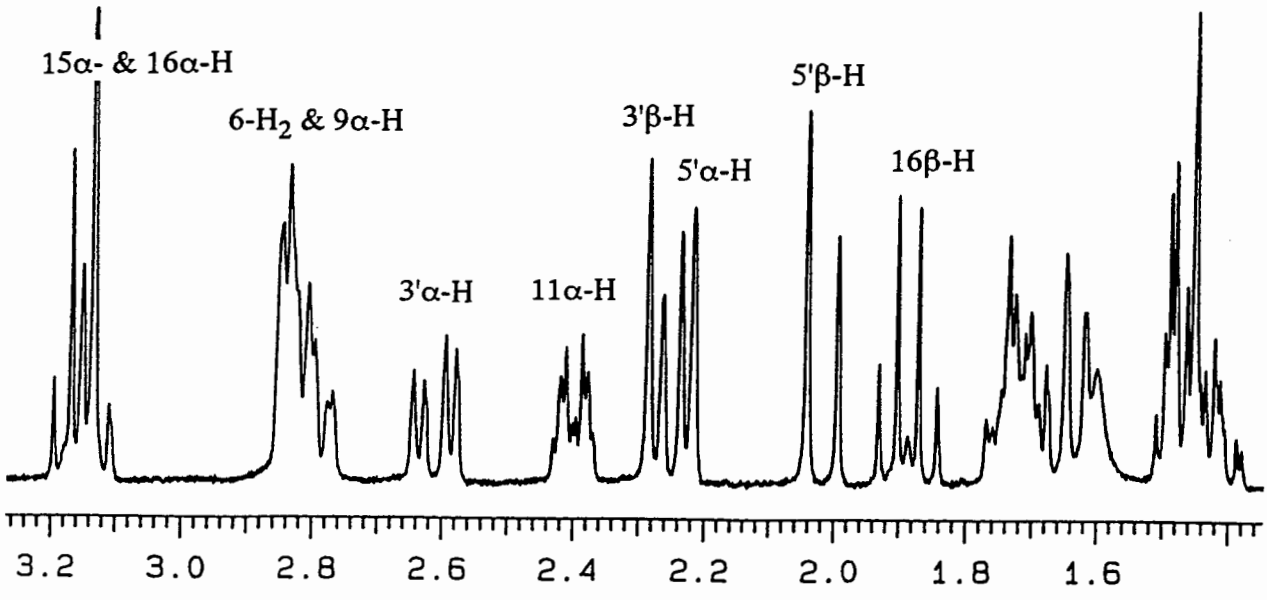


Figure 4.10a: High-field region of ^1H-NMR spectrum of the diketone (**61**) in $CDCl_3$

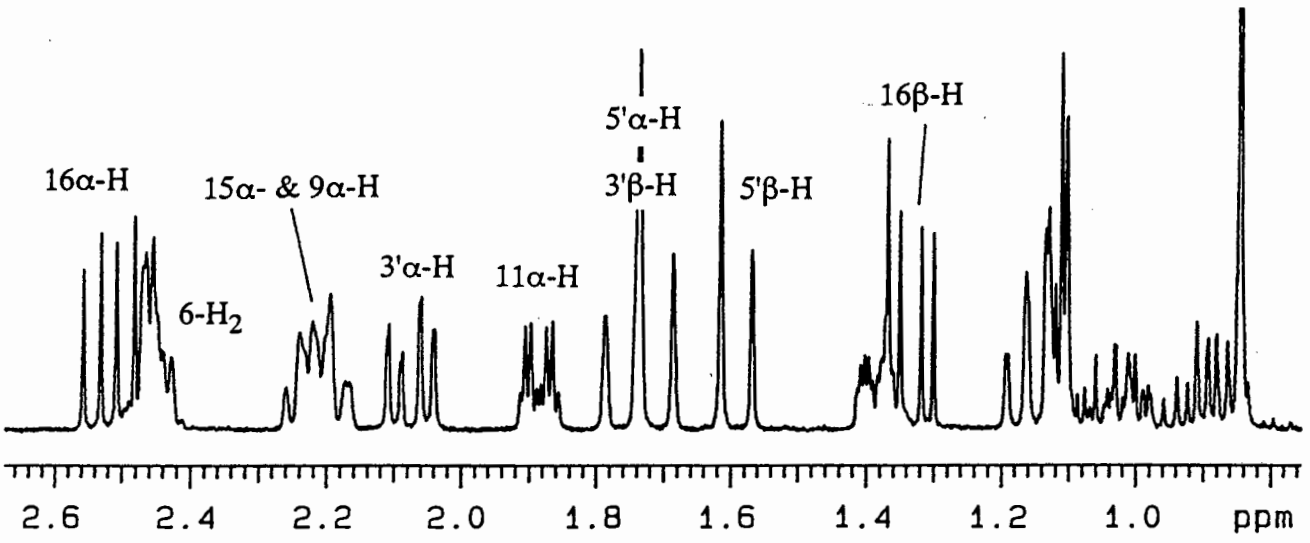


Figure 4.10b: High-field region of ^{1}H-NMR spectrum of the diketone (**61**) in C_6D_6

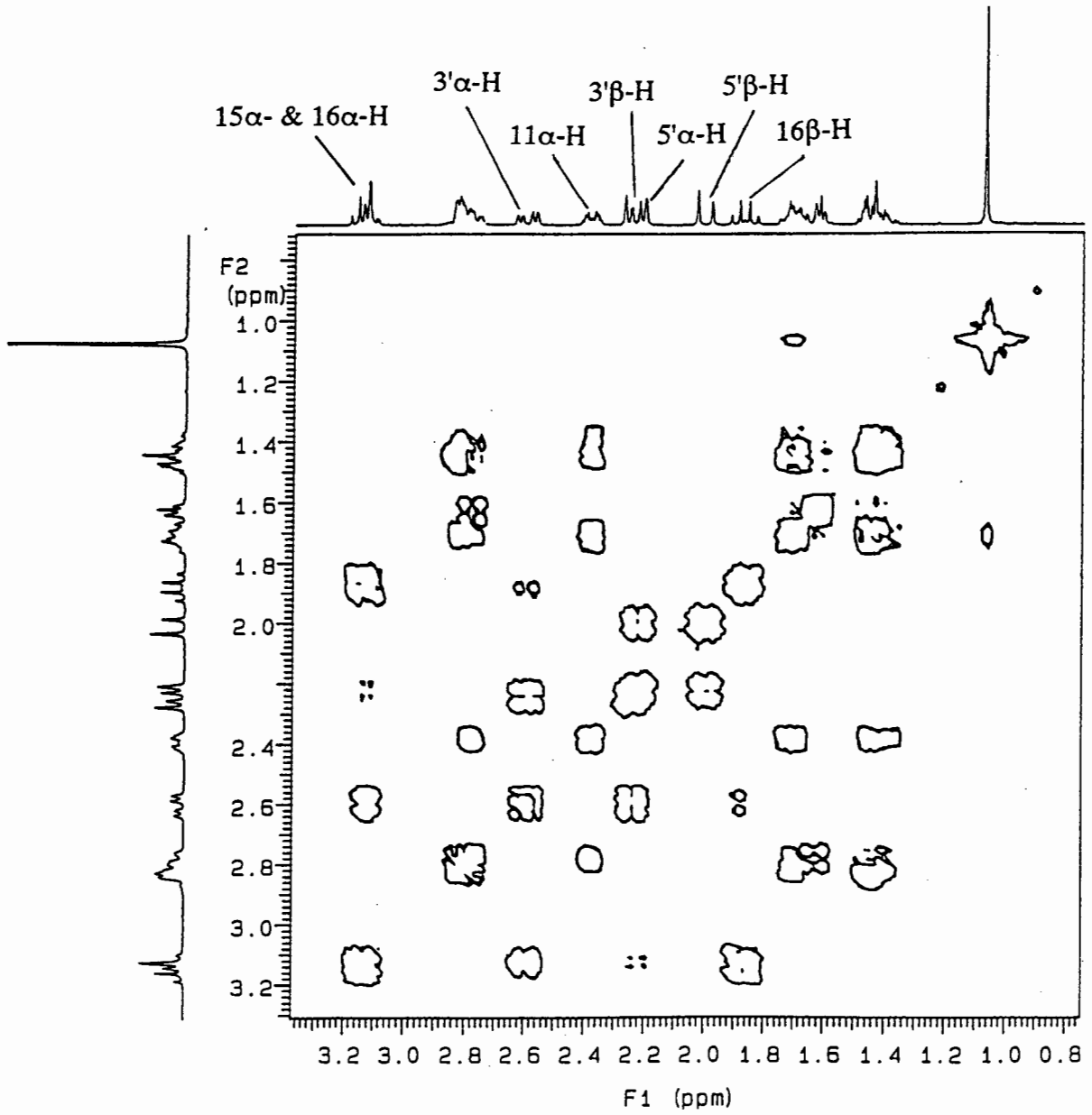


Figure 4.10c: High-field region of COSY spectrum of the diketone (**61**)

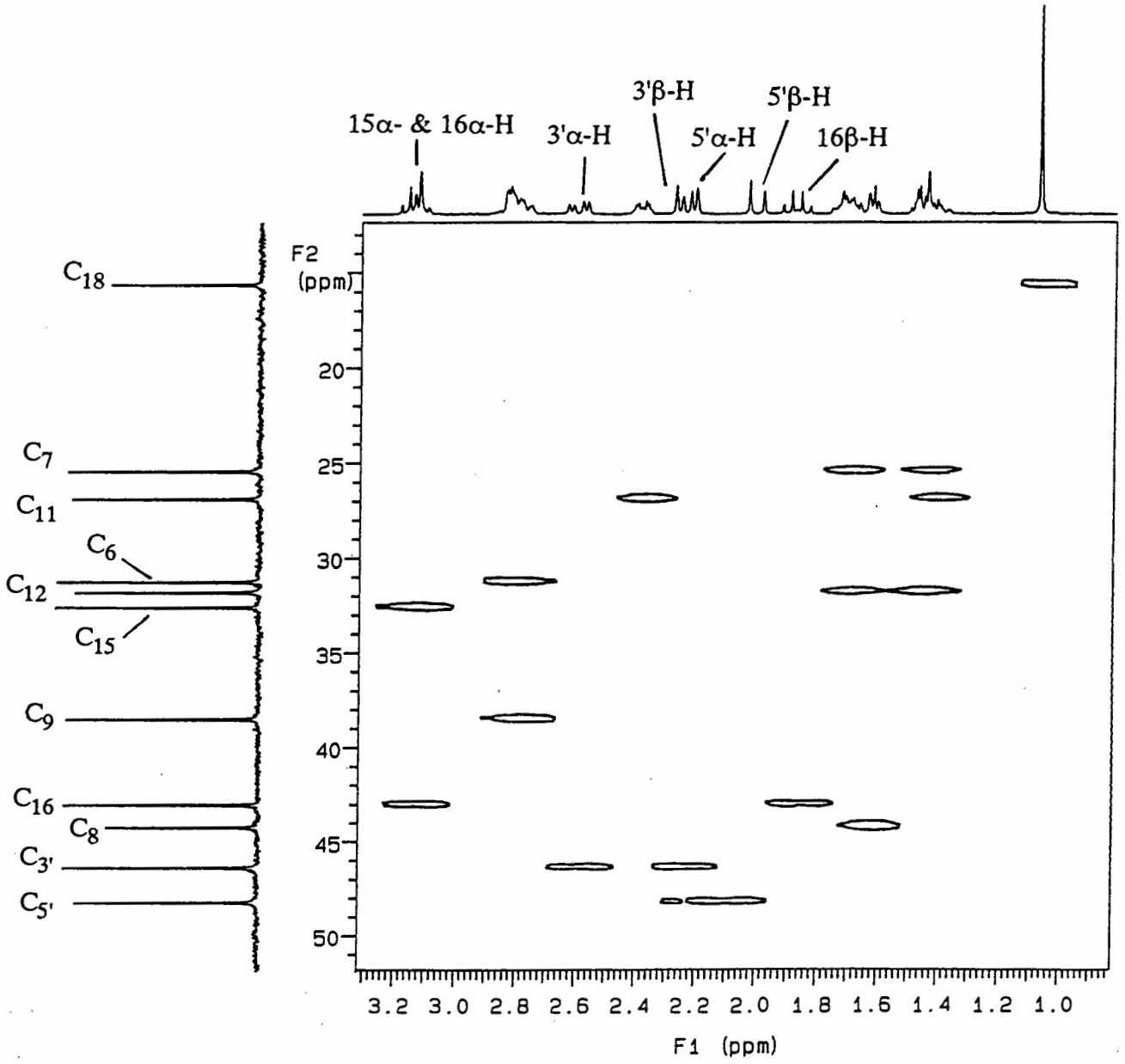


Figure 4.10d: High-field region of HETCOR spectrum of the diketone (**61**)

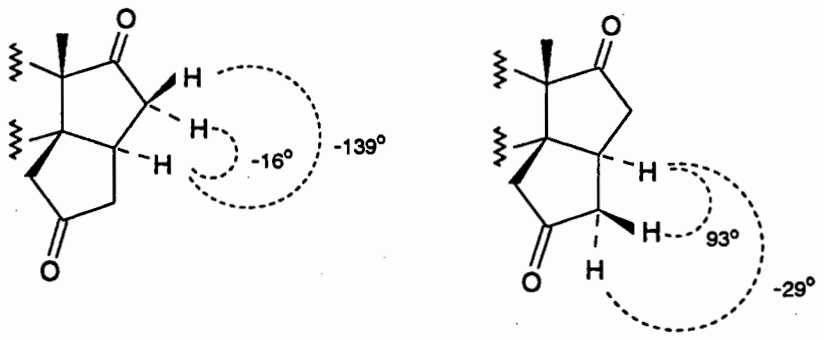
Table 4.11: Ring-D and Ring-E Proton Assignments for Diketone (**61**)[a]

δ /ppm	Int.	Mult.	*J* /Hz	Assignment
$CDCl_3$				
1.87	1H	m	-	16β-H
2.02	1H	d	19	5'β-H
2.24	1H	dd	19, 0.9	5'α-H
2.26	1H	d	19.7	3'β-H
2.62	1H	ddd	19.7, 6.4,1.6	3'α-H
3.14	2H	m	-	15α-& 16α-H
C_6D_6				
1.33	1H	dd	19.8, 7.3	16β-H
1.59	1H	d	19.4	5'β-H
1.71	1H	d	19.3	3'β-H
1.76	1H	dd	19.4, 1.1	5'α-H
2.08	1H	ddd	19.3, 8, 1.1	3'α-H
2.21	1H	m	-	15α-H
2.52	1H	dd	19.8, 10.5	16α-H

[a] Integration (Int.), Multiplicity (Mult.)

The expected AB system for the 5'-protons showed evidence of further long-range coupling. Thus signals at δ 2.02 (d, *J* 19 Hz) and δ 2.24 (dd, *J* 19 and 0.9 Hz) were assigned to 5'β- and 5'α-H respectively. The long-range (0.9 Hz) coupling was ascribed to the four-bond coupling between 5'α-H and 15α-H, evident from a weak crosspeak in the COSY spectrum between the 5'α-H doublet of doublets and the multiplet at δ 3.14. From HETCOR and COSY spectra, the remaining two epimeric pairs of proton signals for C(3') and C(16) were located. One proton was part of the two-proton multiplet at δ 3.14, and its geminal partner resonated at δ 1.87. This high-field signal appeared quartet-like, but resolution enhancement of the signal indicated that it was non-symmetrical and non-first order. The signal at δ 2.62 (ddd, *J* 19.7, 6.4 and 1.6 Hz) had a geminal coupling partner at δ 2.26 (d, *J* 19.7 Hz). These protons could not be unambiguously assigned to the 3'- or 16-position from spectral data alone. Molecular mechanical calculations were thus performed on this, and related, structures. The dihedral angles for the diketone (**61**) are shown in Figure 4.12.

Figure 4.12



	-139°	-16°	93°	-29°
Found (Hz):	7.3	10.5	0	8
Calc (Hz):	6.1	9.5	0.3	7.7

The 93° torsion angle between 15α-H and 3'β-H implies a zero coupling constant. The signal at δ 2.26 (doublet) was thus assigned to 3'β-H, and its epimeric partner, 3'α-H, was therefore assigned the more complex signal at δ 2.62 (ddd, *J* 19.7, 6.4 and 1.6 Hz). The smaller (*J* 6.4 Hz) coupling arose from the vicinal relationship between 3'α-H and 15α-H, and the even smaller (*J* 1.6 Hz) coupling can be attributed to a long-range four-bond coupling to 16β-H, confirmed by a crosspeak in the COSY spectrum. The high-field second-order signal at δ 1.87 was assigned to 16β-H, requiring the 16α-H to resonate as the second component of the two-proton multiplet at δ 3.14.

The stereochemistry of the protons on C(16) was assigned on the basis of a chemical shift comparison with the C_6D_6 spectrum of the diketone (**61**) and with the spectrum of the parent 17-ketone [formed by reducing the 4'-ketone (*cf* section 4.4); molecular mechanical calculations indicated that the dihedral angles for this 17-ketone were comparable to those of the diketone (**61**)].

The C_6D_6 spectrum of the diketone (**61**) was more resolved than the $CDCl_3$ spectrum. The 15α-H signal, however, overlapped with the 9α-H doublet of triplets, giving rise to a two-proton multiplet at δ 2.21. The 16-protons resonated at δ 2.52 (dd, *J* 19.8 and 10.5 Hz, 16α-H) and δ 1.33 (dd, *J* 19.8 and 7.3 Hz, 16β-H). The relative stereochemistry of these protons was assigned from the magnitude of the vicinal couplings to 15α-H; 16α-H has a synperiplanar, and 16β-H an anticlinal, disposition. The 5'-protons again resonated as an ABX multiplet, the 5'β-H at δ 1.59 (d, *J* 19.4 Hz) and the 5'α-H at δ 1.76 (dd, *J* 19.4 and 1.1 Hz), the small coupling arising from a four-bond

coupling with 3'α-H. The orthogonal relationship between 3'β- and 15α-H was again reflected in the simple doublet at δ 1.71 (*J* 19.3 Hz) assigned to 3'β-H. The 3'α-proton was assigned the signal at δ 2.08 (ddd, *J* 19.3, 8 and 1.1 Hz). The vicinal coupling to 15α-H (8 Hz) is comparable to that found in the $CDCl_3$ spectrum. The smallest (1.1 Hz) coupling, however, cannot be assigned to a long-range interaction with 16α-H, as was proposed in the case of the $CDCl_3$ spectrum owing to an absence of a crosspeak with 16α-H in the COSY spectrum in C_6D_6. The magnitude of the four-bond coupling is, however, compatible with the small splitting of the 5'α-H signal. The region in the COSY spectrum in which a crosspeak for such an interaction would be expected was, however, obscured by the large 3'α-3'β crosspeak.

The NMR data were fully supportive of the structure and the expected conformational features of the diketone (**61**). Since this compound was a key intermediate for further work, however, a single crystal X-ray structure determination was performed (see Chapter 8 for crystal data) (Figure 4.13).

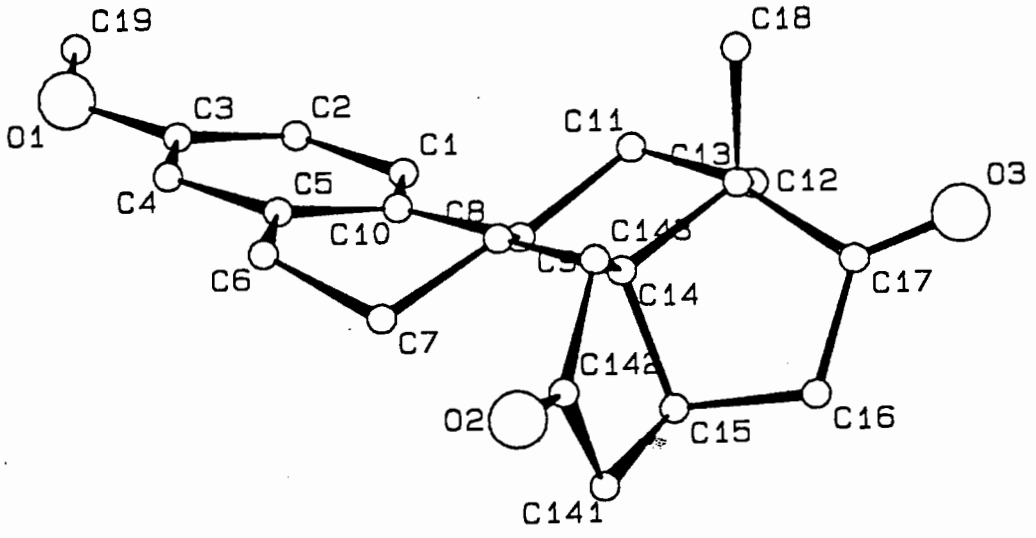


Figure 4.13: X-Ray crystal structure of diketone (**61**) showing crystallographic numbering

The crystal structure displayed no unexpected structural or conformational features. Ring B adopts the conventional 7α,8β-half chair ($^8H_7$) conformation, ring C is a chair ($^8C_{12}$), ring D is an envelope (E_{13}), and the new fused ring has a 'half-chair' conformation ($^{2'}H_{1'}$). A comparison of ring D and E torsion angles indicates the close

correspondance between the solid state structure and the structure predicted by molecular mechanics (Table 4.14).

Table 4.14: Comparison of Selected Actual *vs* Calculated Torsion Angles for the Diketone (**61**)

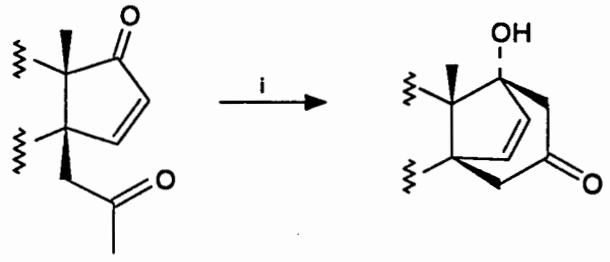
	Torsion Angles (°)	
	Found	Calculated
C(17)-C(16)-C(15)-C(14)	-20	-16
C(17)-C(16)-C(15)-C(3')	-134	-135
C(16)-C(15)-C(14)-C(5')	-85	-90
C(16)-C(15)-C(3')-C(4')	87	94
C(15)-C(14)-C(5')-C(4')	-28	-25
C(15)-C(3')-C(4')-C(5')	8	8
C(3')-C(4')-C(5')-C(14)	14	12
C(3')-C(15)-C(14)-C(5')	34	31
C(17)-C(13)-C(14)-C(15)	-29	-31
C(12)-C(13)-C(14)-C(8)	-41	-50

4.3.1 3-Methoxy-14,17β-propano-14β-estra-1,3,5(10),15-tetraen-17α-ol. The regioselectivity of the base-mediated condensation of the 14β-acetonyl enone (**60**), leading only to the fused ring structure (**61**), is not surprising. It was of interest, however, to ascertain whether the regioselectivity could be influenced in favour of an intramolecular aldol condensation, which would lead to one of the objectives described earlier, *viz.* the Δ^{15}-14β,17β-propanoestradiol (**59**). In order to suppress the Michael reaction of the acetonyl enone (**60**), and to promote this alternative mode of coupling, a cerium(III)-mediated procedure was employed, since it is known that trivalent cerium promotes 1,2-additions to α,β-unsaturated carbonyl systems.[82] This proved successful, since treatment of the acetonyl enone (**60**) with lithium hexamethyldisilazide in the presence of cerium(III) chloride at -50°C gave rise to the desired 17α-hydroxy 17^2-ketone (**64**) in 58% yield (Scheme 4.15).

The spectral characteristics of the hydroxy ketone (**64**) were similar to those of the saturated analogue (**21**) (*cf.* chapter 3), the only differences being due to the AB multiplet at δ 5.82 and 5.94 (each d, *J* 6 Hz) for the 15- and 16-protons, typical of an α-face etheno bridge. The 17^1- and 17^3-protons were assigned to isolated sets of AB multiplets as well, that for the 17^3-protons occurring upfield at δ 2.19 and 2.45 (each d,

J 18.7 Hz) relative to that for the 17^1-protons at δ 2.54 and 2.68 (each d, *J* 17.9 Hz). No further splitting due to long range coupling was observed.

Scheme 4.15



60 **64**

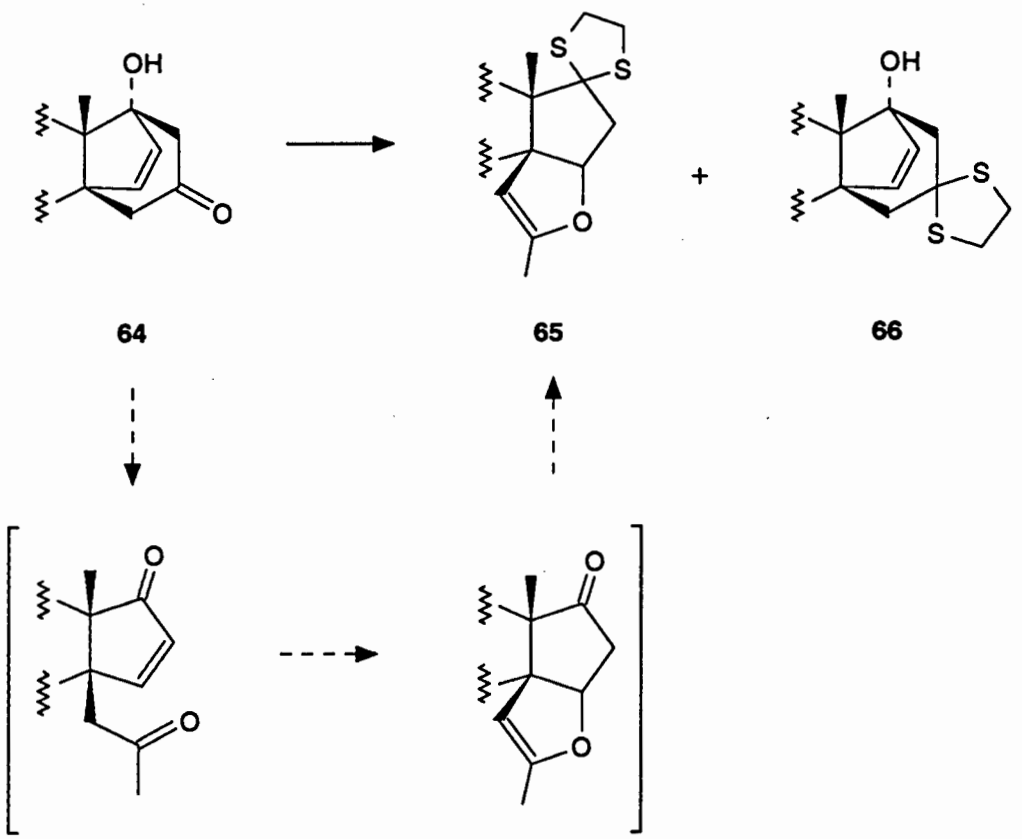
i, LHMDS, $CeCl_3$, -50°

Use of lithium diisopropylamide or lithium hexamethyldisilazide as bases at low temperature in the absence of a Ce^{3+} salt also gave rise to **64**, but as a minor product, thereby indicating the effectiveness of the cerium in promoting 1,2-additions.

This result was satisfactory for the purposes of preparing the parent 14β,17β-propano Δ^{15}-estradiol analogue. Accordingly, the thioketalisation-desulfurisation route used successfully in the preceding chapter was employed to deoxygenate the 17^2-oxo group of hydroxy ketone (**64**). However, treatment of **64** with ethane-1,2-dithiol using zinc triflate as catalyst at 20°C for 1 h, was complicated by the formation of two major products, which were separated and characterised. (Scheme 4.16).

The less polar compound (34% yield) was formulated as the 17,17-dithioketalised dehydrofuran (**65**). The NMR spectrum of the dithioketal (**65**) was similar to that of the furano ketone (**63**). The 5'-methyl group resonated at δ 1.82 as a doublet (*J* 1 Hz), this splitting arising from a four-bond coupling with the 4'-H, which also appeared as a doublet (*J* 1 Hz) at δ 4.26. The thioketal protons resonated at δ 3.16 as the expected four-proton multiplet, and the 15α-H at δ 4.7 as a degenerate doublet (*J* 7.7 Hz). The infrared spectrum exhibited a C=C absorption band for the $\Delta^{4'}$-olefin at ν_{max} 1676 cm^{-1}, and a molecular ion of 414 was in agreement with the proposed structure. Formation of the furano thioketal (**65**) can be explained by acid-catalysed retroaldol opening of the propano bridge, followed by closure in a Michael sense, to yield the acetal, which then underwent thioketalisation (Scheme 4.16).

Scheme 4.16



The more polar product (23% yield) was found to be the desired 17^2,17^2-dithioketal (**66**). Spectroscopic data was consistent with this structure. The ^{1}H-NMR spectrum displayed three isolated AB systems for the 17^1-, 17^3-, and 15- and 16-olefinic protons (Table 4.17), as well as a four-proton multiplet at δ 3.2-3.29 characteristic of a dithioketal.

Table 4.17: NMR Data and Assignments for the AB Multiplets of (**65**)

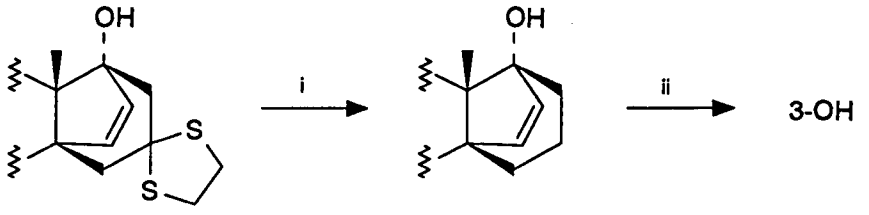
δ /ppm	Int.	Mult.	*J* /Hz	Assignment
2.18 & 2.4	each 1H	d	14.7	17^3-H_2
2.49 & 2.63	each 1H	d	13.9	17^1-H_2
5.89 & 5.97	each 1H	d	6.0	15 & 16-H_2

The failure of the zinc triflate catalysed thioketalisation to proceed more cleanly was unexpected in view of the mildness of the reaction conditions. Somewhat surprisingly, thioketalisation of the hydroxy ketone (**64**) proceeded much more efficiently in the presence of toluene-*p*-sulfonic acid in glacial acetic acid, leading to a superior

yield of the desired thioketal (**66**) (65% as opposed to 23% yield). The quantity of undesired isomer (**65**) isolated was correspondingly decreased (14% as opposed to 34%), and the overall yield of the reaction improved.

Treatment of the thioketal (**66**) with commercially-available Raney nickel (Aldrich, W2) in refluxing ethanol for 2 h yielded the desulfurised compound (**59**) in 58% yield (Scheme 4.18). Spectroscopic data were consistent with this structure.

Scheme 4.18



66 **59** **67**

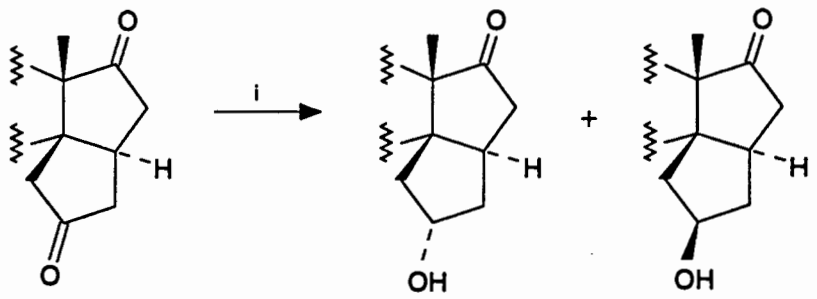
i, Ra-Ni, EtOH, Δ; ii, DIBAH, toluene, Δ

Conventional demethylation of the olefinic alcohol (**59**) using DIBAH in refluxing toluene gave the olefinic diol (**67**) in 76% yield (Scheme 4.18). Analytical data confirmed that deprotection had taken place, and the material was submitted for biological evaluation.

4.3.2 Chemoselective Reduction of the Diketone (61). The novel 14β,15β-fused ring system of the diketone (**61**) constitutes a new structural variant in steroids, and it was of interest to explore the structure and reactivity of the compound. An additional incentive was the possibility of preparing new hormone analogues based upon this structure, and comparing the binding affinities with homologous estradiols which have been shown to display varying affinities for the estradiol receptor.[70,72]

In the first place, the chemoselective reactivity of the diketone was examined. Treatment of the diketone (**61**) with lithium aluminium hydride and sodium borohydride under a variety of conditions gave rise to complex multicomponent mixtures of diols and hydroxyketones. Use of L-Selectride® at lower temperatures (-60 to -50°C), however, resulted in the chemoselective formation of an inseparable mixture (7:3, from NMR) of products (62% yield) formulated as the 4'ξ-hydroxy 17-ketones (**68** and **69**) on the basis of a spectroscopic analysis of the mixture (Scheme 4.19).

Scheme 4.19



61 **68** **69**

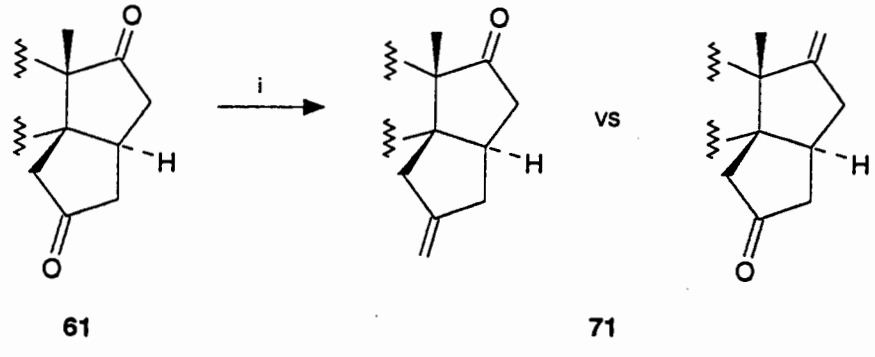
i, L-Selectride

The infrared spectrum of the hydroxy ketone mixture (**68** + **69**) displayed strong hydroxy and carbonyl group absorption bands at ν_{max} 3603 and 1725 cm^{-1} respectively. A low-field signal at δ 4.49 (qd, *J* 3 x 8.7 and 4.7 Hz) in the ^{1}H-NMR spectrum of the mixture was assigned to 4'β-H of the major epimer (**68**). This signal was slightly obscured by the signal at δ 4.6 (td, *J* 2 x 8.1 and 4.4 Hz) for the 4'α-proton of the minor epimer (**69**). Owing to a lack of crystallinity, the major product could not be purified by recrystallisation techniques. Attempted separation of the mixture through acetylation (acetic anhydride in pyridine) failed, giving rise to an inseparable mixture of 4'ξ-acetoxy 17-ketone epimers (**70**). The total acetylation product showed similar spectral characteristics to that of the hydroxy ketone mixture.

The problem of isomer separation notwithstanding, the foregoing reduction gave an encouraging indication of the chemoselectivity of the 4'-oxo group in the diketone (**61**). A Wittig methylenation was carried out in order to test this trend, and to give a more simply characterisable single isomer. (Scheme 4.20).

Treatment of the diketone (**61**) with methyl triphenylphosphorane[83] at reflux for 2 h gave a single, crystalline product, formulated as the methylene ketone (**71**), in good yield (92%). The infrared spectrum of **71** showed a single carbonyl absorption band at 1728 cm^{-1}, and mass spectral and microanalytical data were consistent with monomethylenation of the dicarbonyl system. The high-field regions of the ^{1}H, COSY and HETCOR spectra are illustrated below (Figure 4.21). The spectra were also recorded in C_6D_6 for clarity and comparison with the diketone (**61**), since the structures were isoelectronic.

Scheme 4.20



61 **71**

i, $(PPh)_3CH_2Br$, n-BuLi

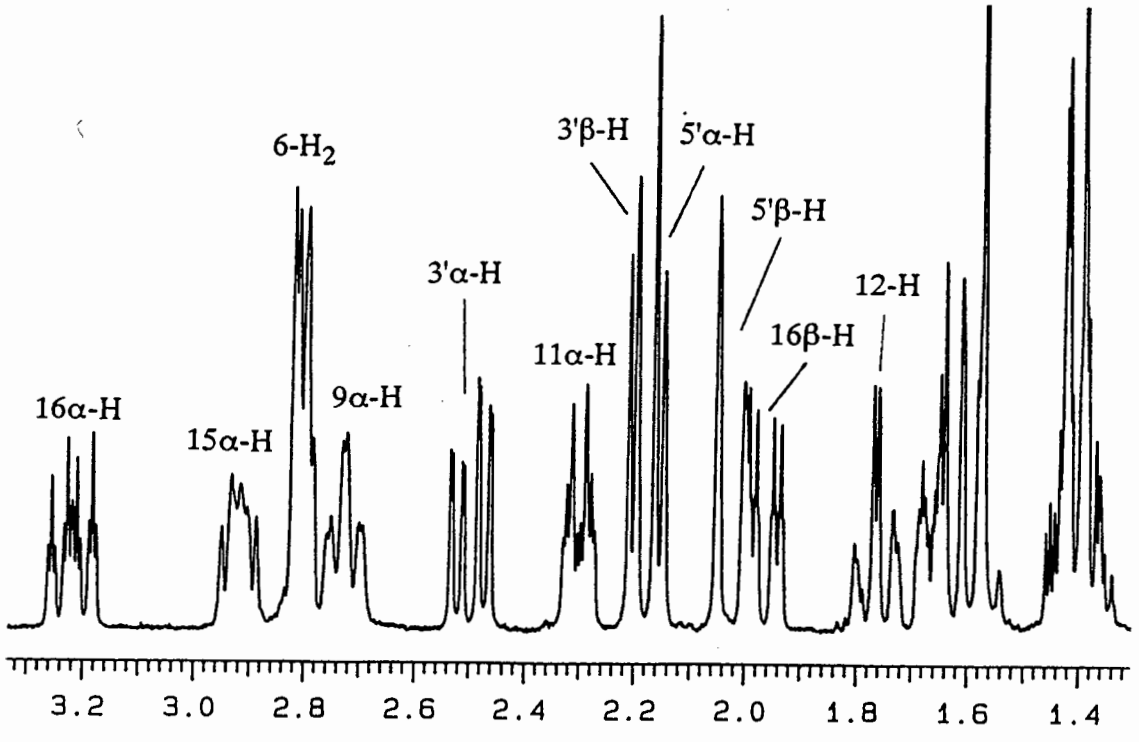
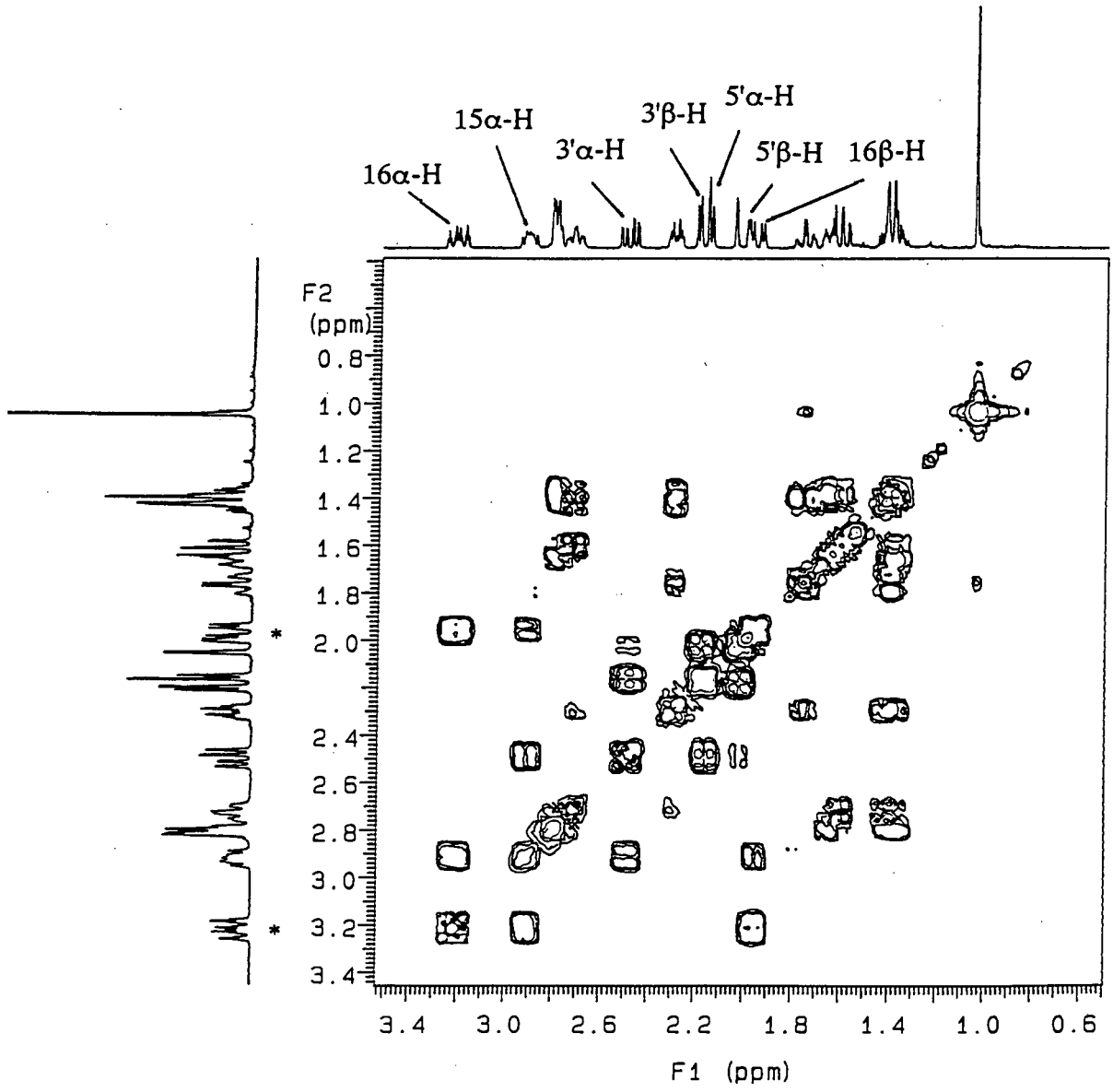


Figure 4.21a: High-field region of ^{1}H-NMR spectrum of the methylene ketone (**71**) in $CDCl_3$



* Crosspeaks with methylene protons to these signals

Figure 4.21b: High-field region of COSY spectrum of the methylene ketone (**71**) in $CDCl_3$

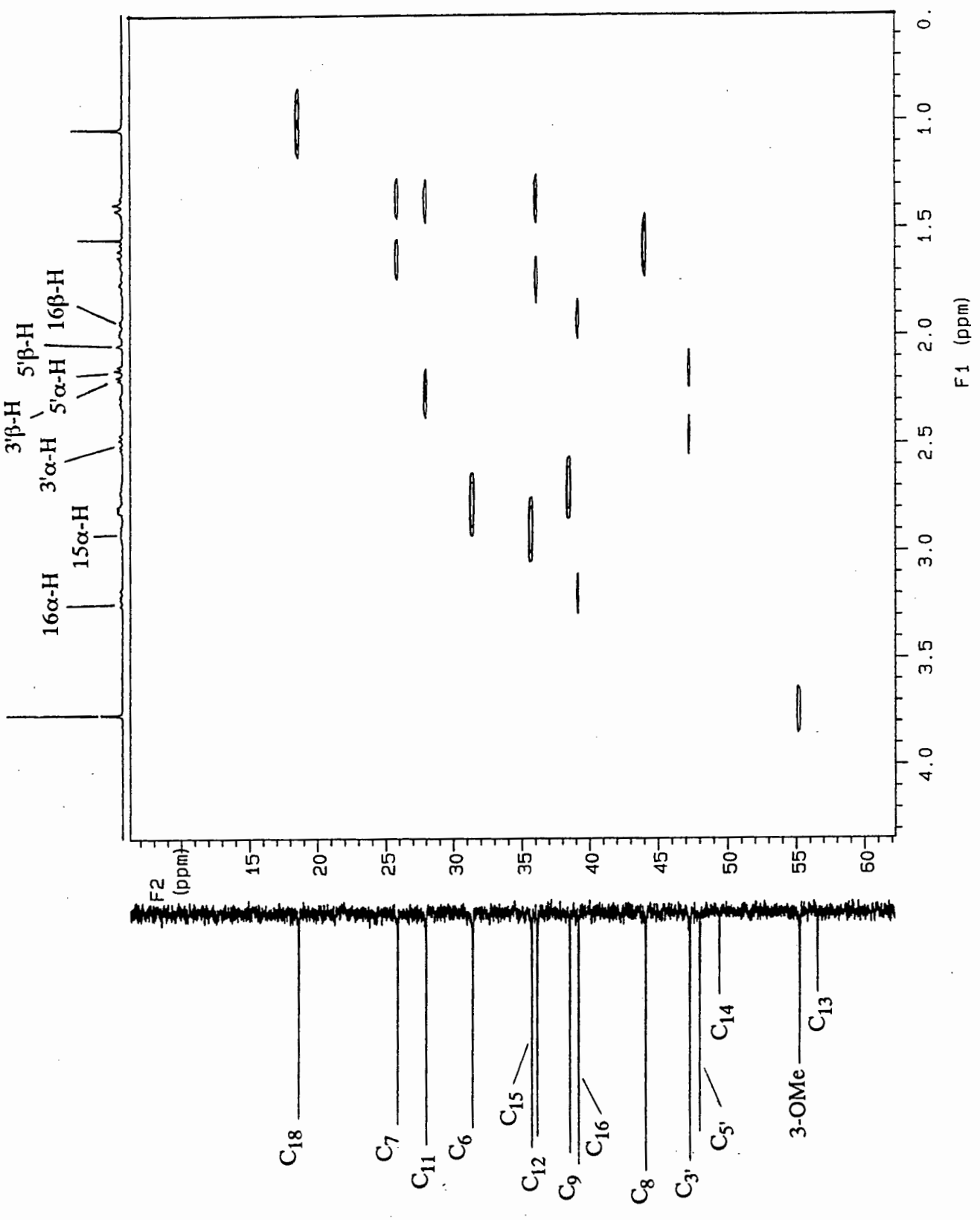


Figure 4.21c: High-field region of HETCOR spectrum of the methylene ketone (**71**) in $CDCl_3$

The methylene protons resonated as a two-proton multiplet at δ 4.83, forming crosspeaks in the COSY spectrum with two multiplets at δ 3.22 (ddt, *J* 17.8, 11.3 and 2 x 3.1 Hz) and δ 1.96 (ddt, *J* 17.8, 5.7 and 2 x 1.5 Hz). These two signals coupled to each other and to a one-proton multiplet at δ 2.9, assigned to 15α-H on the basis of a crosspeak with C(15) in the HETCOR spectrum. The HETCOR spectrum was used to distinguish the disubstituted ^{13}C signals for ring D and E, and hence the epimeric proton pairs on these carbon centres. One set of geminally-coupled protons resonated at δ 2.5 (ddd, *J* 19.7, 8.4 and 1.5 Hz) and δ 2.18 (d, *J* 19.7 Hz), and a closed AB multiplet was observed at δ 2.02 and δ 2.19 (each d, *J* 18.6 Hz) for another epimeric pair. The ring D and E protons were assigned on the basis of spectroscopic comparison with the diketone (**61**) and related structures (Table 4.22).

Table 4.22: NMR Data for Key Diastereotopic Protons in the Methylenation Product (**71**)

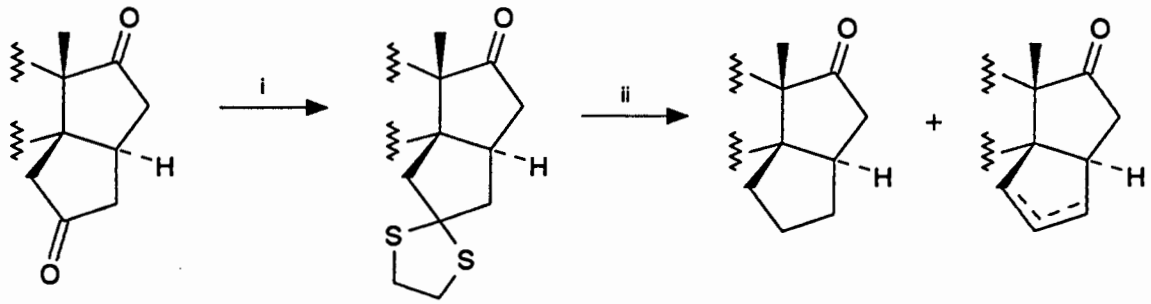
δ /ppm	Mult.	*J* /Hz	Assignment
$CDCl_3$			
1.96	ddt	17.8, 5.7, 2 x 1.5	16β-H
2.02	d	18.6	5'β-H
2.18	d	19.7	3'β-H
2.19	dd	18.6, 1.5	5'α-H
2.5	ddd	19.7, 8.4, 1.5	3'α-H
2.9	m	-	15α-H
3.22	ddt	17.8, 11.3, 2 x 3.1	16α-H
4.83	m	-	4'=CH_2
C_6D_6			
1.58	ddt	17.8, 5.8, 2 x 1.7	16β-H
1.82	dd	18.5, 1.3	5'α-H
1.88	d	19.3	3'β-H
2.01	d	18.5	5'β-H
2.19	ddd	19.3, 8.3, 1.3	3'α-H
2.32	m	-	15α-H
2.83	ddt	17.8, 11.1, 2 x 2.6	16α-H
4.75	m	-	4'=CH_2

It became apparent when attempting to compare the data for the methylene ketone (**71**) with that recorded for the diketone (**61**), that these data were not readily reconcilable. The expected 4'-methylene 17-ketone structure could not explain why the signals assigned to the epimeric 16-protons showed crosspeaks with the 4'-methylene protons in the COSY spectrum. Additionally, if methylenation had taken place at C(4'), then both the 3'- and 5'-protons should exhibit allylic couplings of the order of 0.5-2 Hz to 4'=CH_2. The small (1.5 Hz) for 5'α- and 3'α-H is a mutual long-range coupling, evidenced by a crosspeak in the COSY spectrum, and not an allylic coupling to 4'=CH_2. Furthermore, even if the assignments for the 3'- and 16'-protons were reversed, and it was was assumed that the 5'-protons experienced a zero coupling to 4'=CH_2 and were thus assigned the closed AB multiplet at δ 2.02 and δ 2.19, a discrepancy with the 16-proton signals would arise. The 16β-proton would be required to resonate as a doublet, which would be inconsistent with models, torsion angle calculations, and a comparison with similar 17-ketone structures.

One means of solving this apparent structural problem is to propose a chemoselective reversal ie. methylenation at C(17). The steric bulk of the triphenylphosphonium methylide, however, dictates that this is not an option. According to the mechanism of methylenation, the ylide must lie over the carbonyl group, implying the involvement of stereoelectronic factors. From models, the approach of a triphenylphosphonium methylide to the β-face of the diketone (**61**) is not favourable, owing to the concave nature of the fused ring system, whether at the 4'- or 17-ketone, and an eclipsing interaction with the C(12)-C(13) bond would preclude attack at the α-face of the 17-ketone. The chemoselectivity of the diketone (**61**) consistently favours the more accessible 4'-position under both reduction and thioketalisation conditions (see below), further reinforcing the expected preference for methylenation at the 4'-oxo group of **61**. This problem requires further investigation, including chemical modifications, in order to unambiguously assign the structure.

The essence of this investigation into chemodifferentiation of the oxo groups of the diketone (**61**) was to ascertain the feasibility of selective deoxygenation at C(4'). Attempts to selectively thioketalise the diketone (**61**) using ethane-1,2-dithiol and borontrifluoride-diethylether complex yielded a multicomponent mixture. Milder conditions, employing either zinc triflate or *p*-TsOH as catalysts, however, gave good yields (*ca* 85%) of the singly dithioketalised compound (**72**) (Scheme 4.23).

Scheme 4.23



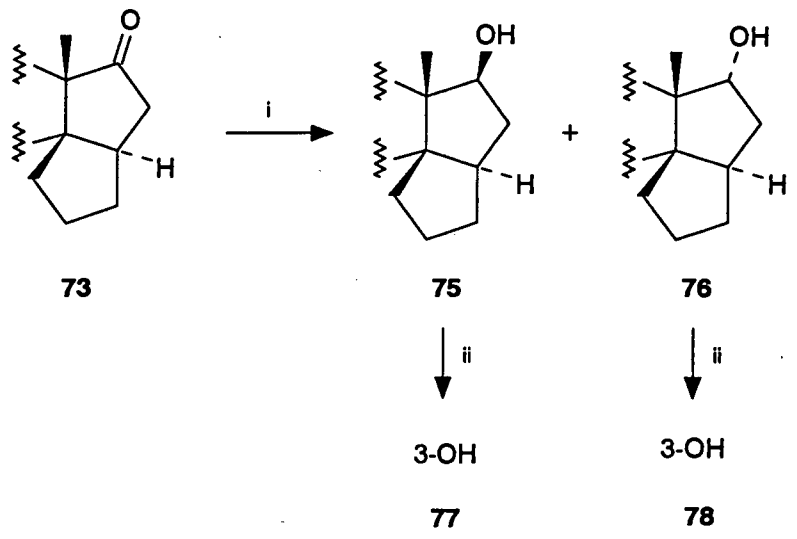
i, $HS(CH_2)_2SH$; ii, Ra-Ni; iii, Pd-C

The only signal of note in the ^{1}H-NMR spectrum of the 4',4'-dithioketal (**72**) was the four-proton dithioketal multiplet at δ 3.25. The 16α- and 16β-proton signals were not unambiguously assignable, since the 16α-H signal was obscured by the 6-H_2 multiplet at δ 2.9 and the epimeric proton signal was obscured in the high-field region of the spectrum. The molecular ion of m/z 414 confirmed that thioketalisation had occurred at only one carbonyl group. Zinc triflate as catalyst allowed for enhanced reaction rates (1.5 h as opposed to 18 h using *p*-TsOH/acetic acid) and easier work-ups, making it the catalyst of choice.

Raney nickel desulfurisation of the thioketal (**72**) in refluxing ethanol proceeded in 84% yield (Scheme 4.23). The desulfurised product (**73**) was, however, accompanied by a trace amount of an impurity caused by elimination of the disulfide moiety. This olefinic impurity (**74**) co-eluted and co-crystallised with the ketone (**73**), so that it was necessary to hydrogenate the entire reaction residue after work-up using Pd/C as catalyst. The small low-field peaks in the olefinic region of the ^{1}H-NMR spectrum were seen to disappear after this hydrogenation. The 16β-proton of the pure ketone (**73**) was assigned the signal at δ 1.76 (dd, *J* 19 and 6.1 Hz), while the 16α-proton signal at δ 2.87 was partially obscured (dd, *J* 19 and 10.2 Hz). The 15α-H multiplet was obscured at δ 2.8 by the 6-H_2 multiplet. These coupling constants are in good agreement with the values found for the diketone (**61**), thereby providing assurance that deoxygenation had taken place at C(4'). The C_6D_6 spectrum of the 17-ketone (**73**) showed improved resolution, allowing a multiplet at δ 2.27 (dt, *J* 10.3 and 2 x 6.5 Hz) to be assigned to the 15α-H. The 16-protons reflected these couplings. Molecular mechanics calculations performed on the 17-ketone (**73**) structure indicated that the dihedral angles between $H_{15\alpha}$-$H_{16\alpha}$ and $H_{15\alpha}$-$H_{16\beta}$ were comparable to those found for the diketone (**61**).

Reduction of the 17-ketone (**73**) with lithium aluminium hydride in tetrahydrofuran at 0°C gave rise to a separable mixture of two epimers, the 17-alcohols (**75**) and (**76**) in 18% and 67% yield respectively (Scheme 4.24).

Scheme 4.24



i, LAH, THF; ii, DIBAH, Δ

These compounds were distinguished and unambiguously assigned by both the mutliplicity and chemical shift of the 17-proton signals in the NMR spectra. The minor epimer (**75**), was assigned 17β-OH stereochemistry by analogy to other 14β-alkyl-17-alcohols,[17,55] 17α-H resonating at δ 3.68 as a doublet of doublets (*J* 7 and 1.1 Hz). The 16α-proton was assigned the signal at δ 2.64 (ddd, *J* 15.1, 11.1 and 7 Hz), and the 16β-proton was located in the high-field region (δ 1.23) of the spectrum by a crosspeak with 16α-H in the COSY spectrum of the alcohol (**75**). From models, the dihedral angle between 17α-H and 16β-H approaches 90°. The COSY spectrum, however, does indicate a weak crosspeak between 17α-H and the obscured region at high-field assigned to 16β-H. The small coupling (*J* 1.1 Hz) in the 17α-proton signal must therefore arise from this interaction with 16β-H.

In the case of the major epimer, the 17α-OH compound (**76**), the 17β-proton resonated at δ 3.93 as a doublet of doublets (*J* 9.5 and 8.9 Hz), the magnitude of the vicinal couplings again in agreement with analogous systems described in the literature. 16β-H was clearly visible at δ 1.98 (ddd, *J* 13.7, 11.5 and 9.5 Hz), while the 16α-H signal was again obscured in the high-field region (δ 1.52) and located by a crosspeak with 16α-H in the COSY spectrum. COSY and HETCOR spectra also allowed the 15α-H to be located as a multiplet at δ 1.3.

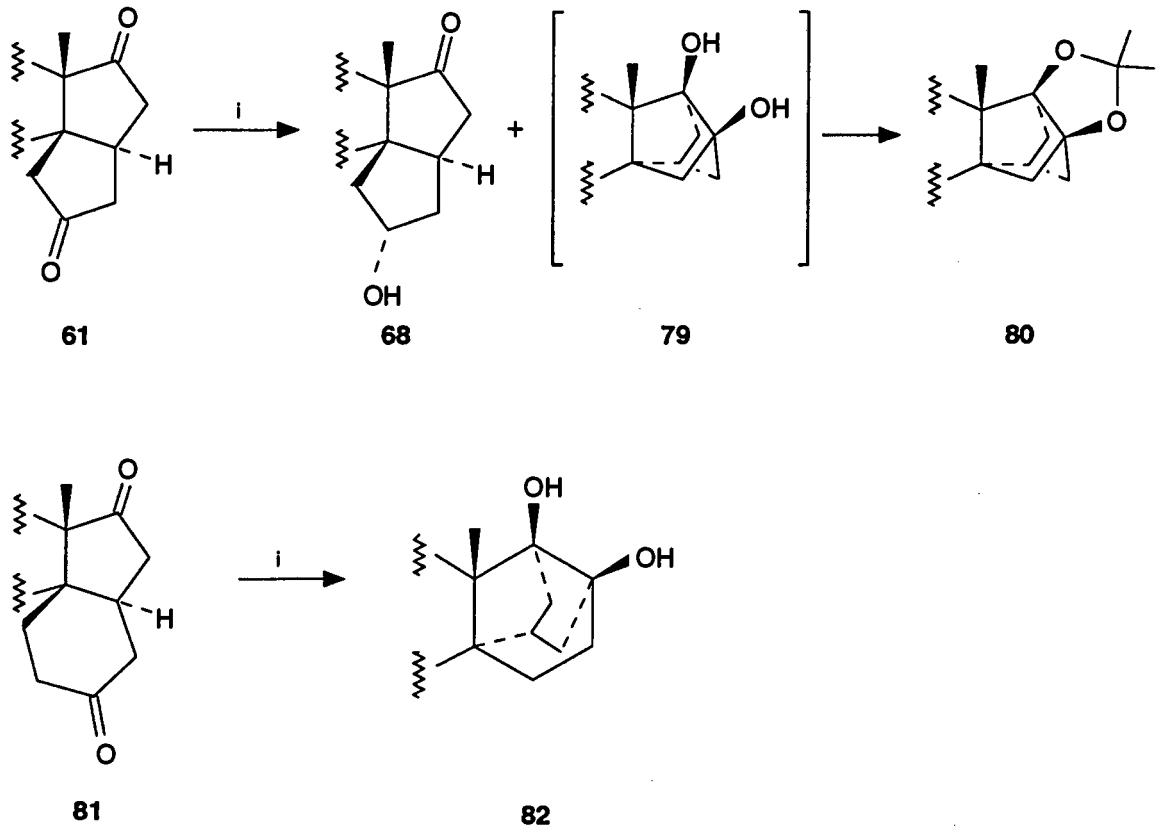
The simplicity of the 17-proton signal in both alcohols (**75**) and (**76**) confirms that the initial deoxygenation of the diketone system (**61**) was regioselective for the 4'-oxo group. If deoxygenation had taken place at C(17), subsequent reduction of the 4'-oxo group would have resulted in each epimeric 4'-H having four vicinal coupling partners.

Standard deprotection of the alcohols (**75**) and (**76**) with DIBAH in refluxing toluene gave rise to the estradiol analogues (**77**) and (**78**) in high yield (Scheme 4.24). These novel 14β,15β-fused ring derivatives were submitted for biological evaluation.

4.3.3 Attempted Reductive Coupling of the Diketone (61). A recent report by Hoffmann *et al.*[84] on the samarium(II) iodide-promoted reductive coupling of *cis*-1,5-dimethylbicyclo[3.3.0]octan-3,7-dione leading to the highly strained 1,5-dihydroxy-3,7-dimethyl[3.3.0.0^{3,7}]octane suggested that the diketone (**61**) might be induced to undergo a similar intramolecular coupling, leading to a novel ring D caged estriol analogue (**79**) (Scheme 4.25). The diol would be interesting in terms of structure-activity studies, since the coupling would create a new ring D of similar orientation to that found in estradiol. Additionally, the 14,17-bridge would closely mimic the 14,17-ethano bridge found in the active 14,17-ethano estradiol analogue. It would be of interest to see if this system could be synthesised in view of the strain the extra 16α,17^{2}-methano bridge would create. A homologous 14β,15β-fused ring system (**81**) did demonstrate the ability to couple in this manner using Hoffman's conditions (Scheme 4.25).[70]

Treatment of the diketone (**61**) with samarium(II) iodide in refluxing tetrahydrofuran for 17 h yielded a crystalline residue which, on chromatography, gave only mixed fractions of polar material. Treatment of the mixed fractions with aqueous (6%) sodium periodate in ethanol at 20°C for 30 min gave diketone (**61**) and hydroxy ketone (**68**), indicating that the mixture probably contained the product of intramolecular coupling, along with the 4'-hydroxy 17-ketone. Reductions of this nature are not without analogy.[85] The components of the periodate cleavage mixture were separated and the hydroxy ketone (**68**) fully characterised. A signal at δ 4.49 in the ^{1}H-NMR spectrum of **68** was assigned to the 4'β-H (qd, *J* 3 x 8.7 and 4.7 Hz). The stereochemistry at C(4') followed from this multiplicity and the magnitude of the couplings. A 4'α-H would give rise to two very small ($J_{4'\alpha,3'\beta}$ and $J_{4'\alpha,5'\beta}$ both close to orthogonal) and two medium-sized couplings ($J_{4'\alpha,3'\alpha}$ and $J_{4'\alpha,5'\alpha}$ both 30-60°). A reversal in configurational assignment, however, would demand that 4'β-H exhibit four medium-to-large interactions with the vicinal protons. Reduction at C(17) was excluded on the basis of the complexity of this signal, thereby confirming the chemoselectivity of this reduction, and

Scheme 4.25



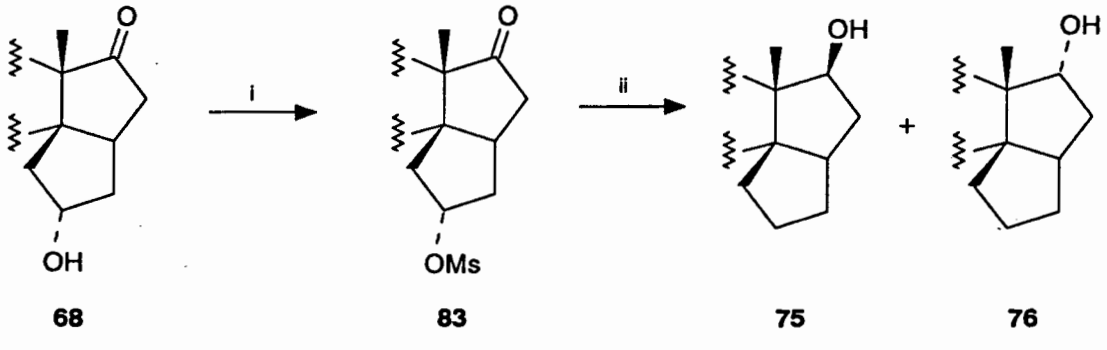
further validating the chemodifferentiation of the diketone (**61**) in the thioketalisation-desulfurisation-reduction route to the estradiol analogues (**75** and **76**). The hydroxy ketone (**68**) was untainted by the epimeric compound (**69**) formed on L-Selectride® reduction of the diketone (**61**) (*cf.* section 4.3.2), indicating the high stereoselectivity of the SmI_2-mediated reduction.

Exposure of the mixed fractions to 70% aqueous perchloric acid in acetone at 20°C for 4 h, gave rise to a separable multicomponent mixture of acetonide (**80**) (8%), diketone (**61**) (13%), and hydroxy ketone (**68**) (60%) (Scheme 4.25). The structure of the acetonide (**74**) was consistent with the presence of two methyl singlets at δ 1.54 and 1.55 in the ^{1}H-NMR spectrum and the absence of other low-field signals. Other spectroscopic and analytical data all support the acetonide structure. The low yield of acetonide (**74**) is unsurprising in view of the strain involved in forming the glycol, as well as the competing reduction of the diketone (**61**) to the hydroxy ketone (**68**). An attempt to force this pinacol-type coupling of diketone (**61**) using the low-valent titanium McMurry

reagent [$TiCl_3(DME)_{1.5}$/Zn-Cu] referred to previously (Chapter 3), even under prolonged reflux, was totally unsuccessful.

Removal of the Hydroxy Group of Hydroxy Ketone (68). Hydroxy ketone (**68**) was expected to undergo a mesylation-reductive displacement sequence which would deoxygenate C(4') with concomitant reduction of the ring D ketone. Treatment of **68** with methanesulfonyl chloride (mesyl chloride) in pyridine at 0°C for 2 h gave rise to a compound formulated as the mesyloxy ketone (**83**); an m/z of 418 was consistent with the expected structure. Lithium aluminium hydride reduction of this material in refluxing toluene for 2 h gave a mixture of 17β- and 17α-hydroxy compounds (**75**) (18%) and (**76**) (47%) (Scheme 4.26).

Scheme 4.26



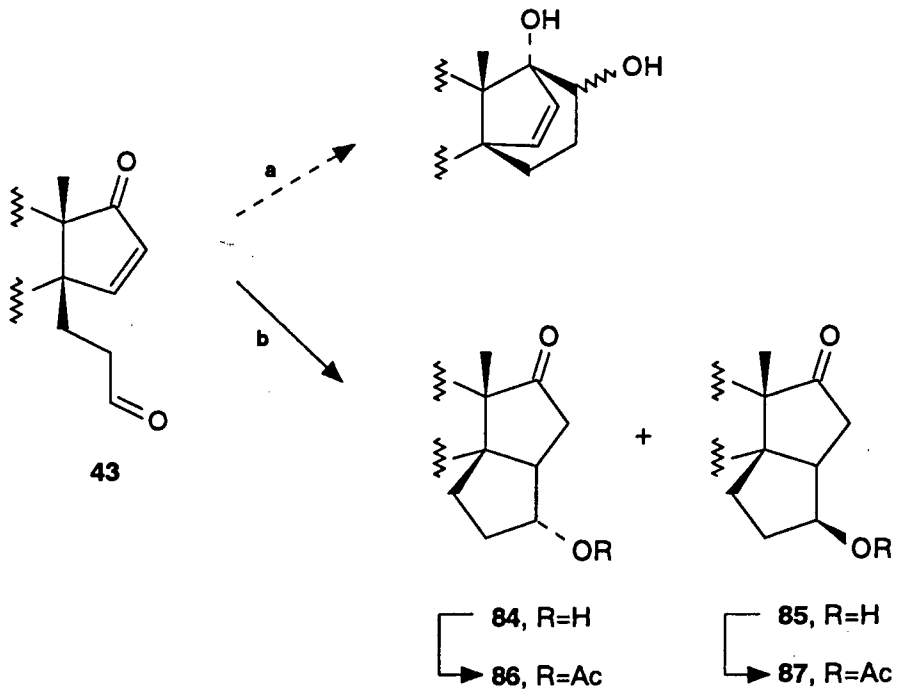
68 **83** **75** **76**

i, MsCl, pyridine; LAH, Δ

4.4 Intramolecular Reductive Coupling of 3-Methoxy-14-formylethyl-14β-estra-1,3,5(10),15-tetraen-17-one (43)

Treatment of the formylethyl enone (**43**), isolated from the Wacker reaction performed on the allyl enone (**17**), with the McMurry reagent as described previously (*cf* Chapter 3) was expected to give rise to reductive coupling. Two modes of intramolecular coupling could be envisaged. A pinacol-type coupling between the two carbonyl groups would give rise to olefinic diols analogous to the result obtained with the saturated formlethyl ketone (*cf.* Chapter 3) (Scheme 4.27, a). Alternatively, vinylogous reductive coupling between the 14^2-formyl group and the ring enone would produce the hydroxy ketones (**84**) and (**85**) (Scheme 4.27, b).

Scheme 4.27



The reaction of the formylethyl enone (**43**) with $TiCl_3.(DME)_{1.5}$ and zinc-copper couple in dimethoxyethane (DME) was complete after 30 min at 0-5°C. The products isolated were identified as a partially separable mixture (3:7 ratio, from NMR) of the hydroxy ketones (**84**) and (**85**) in 85% overall yield. In order to facilitate the assignments of the relevant NMR signals, the monoacetylated derivatives of (**84**) and (**85**), *viz.* 3'-acetoxy 17-ketones (**86**) and (**87**) respectively, were formed under conventional conditions (acetic anhydride, pyridine) (Scheme 4.27). The key NMR data are tabulated below (Table 4.28).

The 3'-proton signals are configurationally diagnostic. Models indicate that a 3'α-OR configuration would give rise to two very small and one medium-sized vicinal coupling. The 3'β-OR configuration, however, would require three medium-sized (*ca* 7-9 Hz) couplings. Thus the minor hydroxy ketone (**84**) was assigned 3'α-OH stereochemistry, and the major epimer (**85**) 3'β-OH configuration.

In terms of face selectivity, the major coupling product (**85**) is interpreted as arising from a like-like interaction in the transition state. From models, it can be seen how the line-up of the *re*-faces of C(14^3) and C(15) leads to a favourable dipole alignment of the two carbonyl groups, giving rise to 3'β-OH configuration in the product (Figure 4.29). This dipole effect is somewhat attenuated since it is not the two carbonyl groups that directly align in the transition state, but rather the formyl group and the ring

enone olefinic bond; this explains the low stereoselectivity of the coupling (3:7 mixture of isomers).

Table 4.28: Diagnostic Signals in the NMR Spectra of the 3'-Alkoxy 17-Ketones (**84-87**)

Proton	Compound			
	84	**85**	**86**	**87**
16α-H	δ 3.05 (dd, *J* 19.5 & 11.2 Hz)	δ 2.64 (dd, 20.2 & 10 Hz)	δ 3.12 (dd, *J* 20 & 11.3 Hz)	δ 2.59 (dd, *J* 20.1 & 10 Hz)
16β-H	δ 1.77 (dd, *J* 19.5 & 5.8 Hz)	δ 2.41 (dd, *J* 20.2 & 6.8 Hz)	δ 1.85 (dd, *J* 20 & 4.4 Hz)	δ 2.27 (dd, *J* 20.1 & 6.9 Hz
15α-H	δ 2.72 (m)	δ 2.93 (dt, *J* 10 & 2 x 6.8 Hz)	δ 2.83 (m)	δ 3.12 (dt, *J* 10 & 2 x 6.9 Hz)
3'α-H	-	δ 4.62 (ddd, *J* 8.7, 7.7 & 6.8 Hz)	-	δ 5.28 (dt, *J* 9.3 & 2 x 6.9 Hz)
3'β-H	δ 4.24 (dd, *J* 7.6 & 2.6 Hz)	-	δ 4.97 (dd, *J* 8 & 2.3 Hz)	-

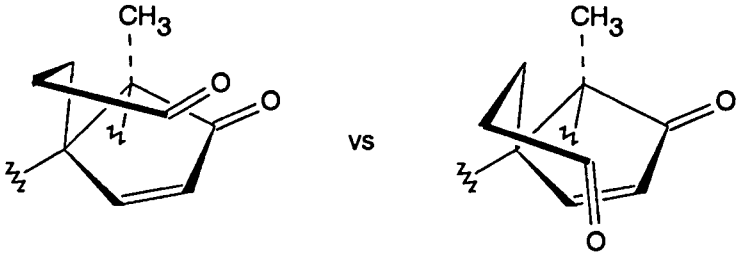
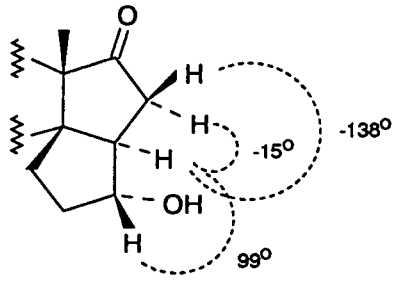


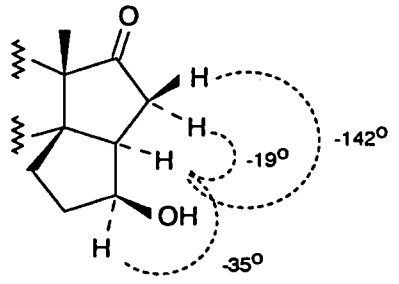
Figure 4.29: Face selectivity in reductive cyclisation of (**43**)

The characteristics of the 15α-H/16α-H and 15α-H/16β-H interactions are consistent throughout this series of cyclopropa[14,15] fused compounds. This is further borne out by the NMR data for the 3'-alkoxy 17-ketones (Table 4.28) in which the 15α-H/16α-H vicinal coupling is again larger in magnitude than the corresponding 15α-H/16β-H coupling. Additionally, the 16α-proton consistently resonates at lower field than the 16β-proton for this series.

The coupling constants for the 3'-hydroxy 17-ketones (**84**) and (**85**) were in agreement with the dihedral angles calculated by a molecular mechanics analysis of the structures (Figure 4.30). As expected, there is also a strong correlation between the torsion angles in these molecules and the previously discussed 17-ketone analogues.



84



85

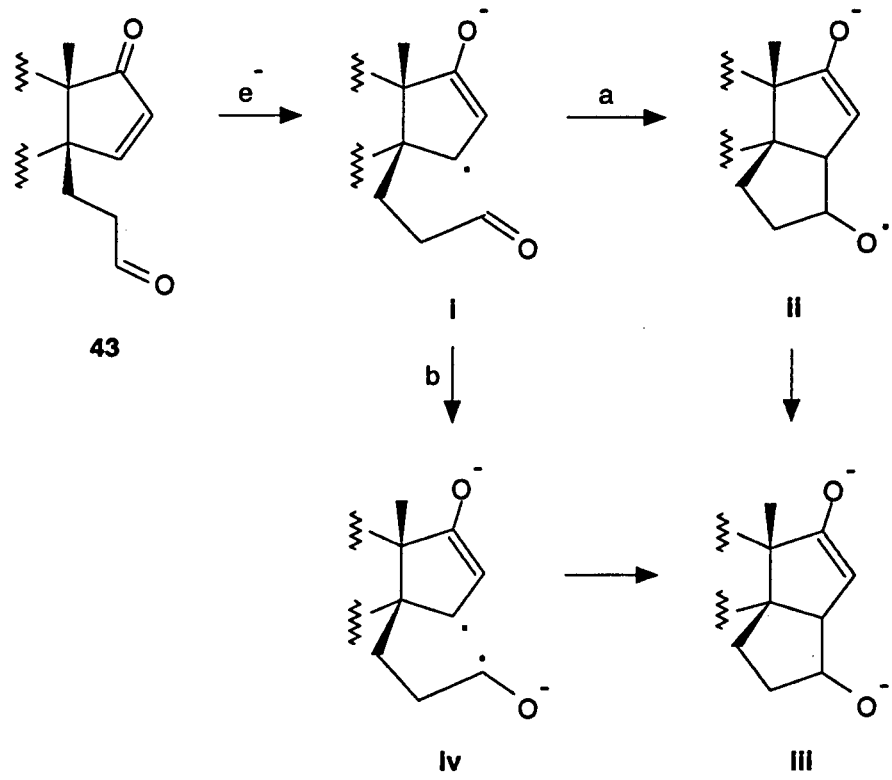
84	-138°	-15°	99°
Found (Hz):	5.8	11.2	2.6
Calc (Hz):	6.0	9.6	1.9

85	-142°	-19°	-35°
Found (Hz):	6.8	10	6.8
Calc (Hz):	6.5	9.1	6.5

Figure 4.30: Coupling constants (*J* /Hz) for hydroxy ketones (**84**) and (**85**)

This vinylogous coupling can be interpreted as proceeding via an initial one-electron addition to the ring enone. The resultant radical anion (**i**) may then attack the 14^3-oxo group, and a subsequent one electron addition to the radical anion (**ii**) so formed generates the dianion (**iii**) (Scheme 4.31, route a). Alternatively, a second one-electron addition to the 14^3-oxo group could take place, followed by coupling of the two radical centres of the diradical dianion (**iv**) to form the dianion (**iii**) (Scheme 4.30, route b).

Scheme 4.31

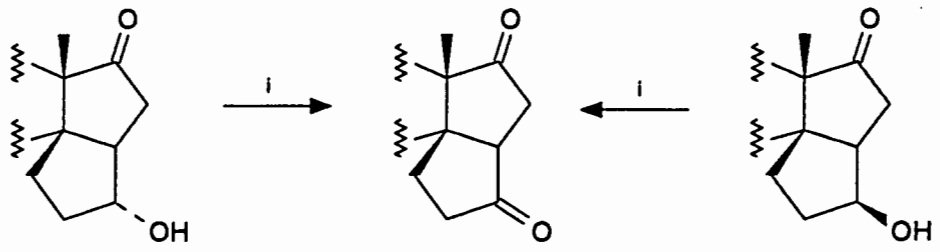


Although the actual sequence of electron addition is not known, there is ample literature analogy for this type of vinylogous coupling,[86] usually involving samarium(II) iodide as a one-electron source.[87] Interestingly, our attempt to use SmI_2 to achieve a similar vinylogous coupling with the formylethyl enone (**43**) was unsuccessful, leading to multicomponent mixtures.

The hydroxy ketones (**84** and **85**) were convertible individually or as an epimeric mixture into the corresponding 17,3'-diketone (**88**) in high yield (89%) under Swern oxidation conditions (Scheme 4.32).

The infrared spectrum of the product, **88**, showed a single broad band at ν_{max} 1732 cm^{-1} for the carbonyl groups. An in-depth spectroscopic analysis was performed on the diketone (**88**) in order to corroborate previous assignments of this cyclopenta[14,15] fused ring system. The HETCOR spectrum allowed for the assignment of C(15) and hence 15α-H. This was part of a two-proton multiplet at δ 3.04, reminiscent of that seen in the $CDCl_3$ spectrum of the diketone (**61**). The other proton signal in this multiplet formed a crosspeak in the COSY spectrum with a second order multiplet at δ 2.05, similar to the apparent 'quartet' found with **61**. These signals were assigned to 16α- and 16β-H respectively. The protons on C(4') were identified at δ 2.41 (dd, *J* 20.2 and 9.6 Hz, 4'β-H) and δ 2.52 (ddd, *J* 20.2, 11.6 and 3.2 Hz, 4'α-H). Both signals were partially

Scheme 4.32



84 **88** **85**

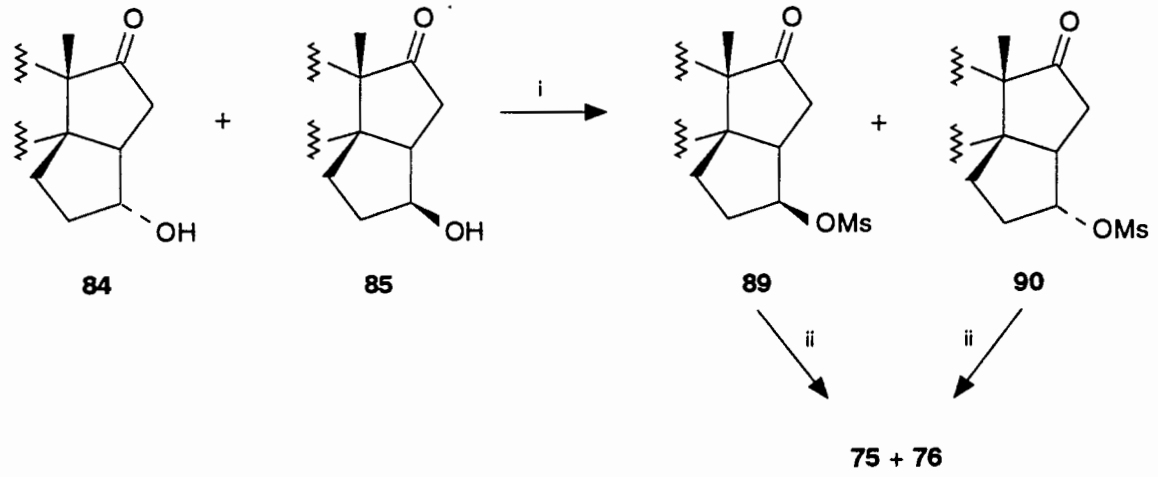
i, DMSO, $COCl_2$

obscured by the 11α- and 9α-H multiplets respectively. The higher-field doublet of doublets was assigned to 4'β-H, the absence of further coupling arising from an orthogonal relationship between the 4'β- and 5'α-protons. The 5'-protons were located by crosspeaks in the COSY and HETCOR spectra as multiplets at δ 1.8 (obsc) and δ 1.93 (ddd, *J* 13.5, 9.6 and 3 Hz). The 9.6 Hz coupling identified the signal at δ 1.93 as arising from 5'β-H. The C_6D_6 spectrum of the diketone (**88**) was not as resolved as that recorded using $CDCl_3$ as solvent.

4.4.1 Removal of the 3'-Hydroxy Groups of Hydroxy Ketones (84) and (85). The reductive coupling approach thus provided an alternative route to the β-face cyclopenta[14,15] fused ring series. The correlation of products derived from both forms of closure was desirable, not only to confirm the structures of intermediates, but also in order to demonstrate the feasibility of using either or both reaction pathways to synthesise hormone analogues. The approach adopted for this purpose was to treat the mixture of 3'-hydroxy 17-ketones (**84** + **85**) with methanesulfonyl chloride in pyridine, and to expose the derived mesylates to lithium aluminium hydride, which was expected to deoxygenate C(3') with concomitant reduction of the 17-oxo group. This would provide a direct route to the estradiol analogues (**75**) and (**76**), in a similar manner to that demonstrated for the 4'α-hydroxy 17-ketone (**68**) (*cf.* section 4.3.3).

For practical purposes, owing to the difficulty in separating the hydroxy ketones (**84** + **85**), treatment of a mixture (3:7) of the hydroxy ketones with mesyl chloride in pyridine at 0°C for 30 min gave rise to the derived mesyloxy compounds (**89**) and (**90**), which were readily separable, in 48% and 22% yield respectively (Scheme 4.33).

Scheme 4.33



i, MsCl; ii, LAH, Δ

The less polar 3'β-OMs compound (**89**) showed spectral characteristics comparable to those of the more polar starting material (**85**). The 3'α-H signal resonated in the expected downfield region, at δ 5.32 (ddd, *J* 14.4, 8.1 and 6.8 Hz). This signal was better resolved than in the hydroxy ketone (**85**). The 15α-proton resonated as a doublet of triplets at δ 3.18 (*J* 10 and 2 x 6.8 Hz), and the 16-protons were discernable at δ 2.31 (dd, *J* 20.1 and 6.8 Hz, 16β-H) and 2.74 (dd, *J* 20.1 and 10 Hz, 16α-H).

The ^{1}H-NMR spectrum of the epimeric mesylate (**90**) was not as well-resolved as that described above for **89**. The 3'β-proton signal resonated at δ 5.0 (dd, *J* 7.7 and 2.7 Hz), the coupling pattern simplified owing to an orthogonal orientation with respect to 4'α-H.

Reduction of both mesyloxy ketones (**89**) and (**90**) separately with lithium aluminium hydride in refluxing tetrahydrofuran gave rise to the alcohols (**75**) and (**76**) in approximately a 1:5 ratio (from NMR). The 3'β-OMs epimer (**89**) required prolonged reaction periods to undergo the reductive diplacement, so that, even after 5 h, some intermediate polar material (possibly the 3'β-mesyloxy 17-alcohol) was still present. With the 3'α-OMs epimer (**90**), the reaction was complete after 2 h.

4.5 Conclusions

The reaction sequence described in this chapter demonstrated that, although Wacker oxidation of the 14β-allyl Δ^{15}-17-ketone (**17**) is not regioselective, both of the resultant products serve as intermediates for the synthesis of the new steroidal fused

cyclopenta[14,15] ring system. Additionally, either pathway has been shown to provide access to the corresponding estradiol analogues. Furthermore, regiocontrolled aldol condensation of the 14β-acetonyl enone (**60**) gave rise to the 14,17β-propano Δ^{15}-estradiol analogue. These hormone analogues were submitted for biological evaluation as competitive binders at the estrogen receptor.

Chapter 5

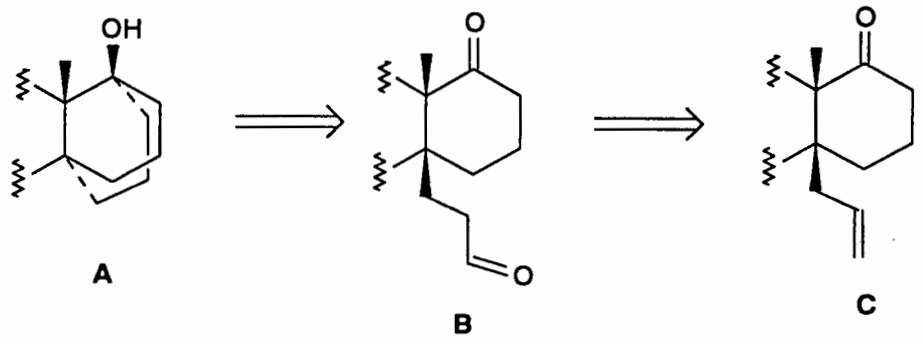
APPROACHES TO THE SYNTHESIS OF 14-ALLYL-3-METHOXY-14ξ-17a-HOMOESTRA-1,3,5(10)-TRIEN-17a-ONE

5.1 Introduction

An important outcome of the work described in chapters 3 and 4 was the finding that the 14β,17β-propano bridge is incompatible with high binding affinity towards the estradiol receptor (*cf.* chapter 6). This contrasts with the favourable structure-activity patterns observed in the 14α,17α-propano series,[16] and provides an indication of the sensitivity of the substrate-receptor interaction towards subtle steric changes in ring D. A useful model for gaining further insight into structure-activity relationships in ring D bridged hormones can be envisaged by combining the propano bridge on each face to form 14,17aα-propano-17a-homoestra-1,3,5(10)-triene-3,17aβ-diol. The biological properties of such a hormone analogue would give a first indication of whether one or the other of the bridge elements is an active prerequisite for high or low binding affinity.

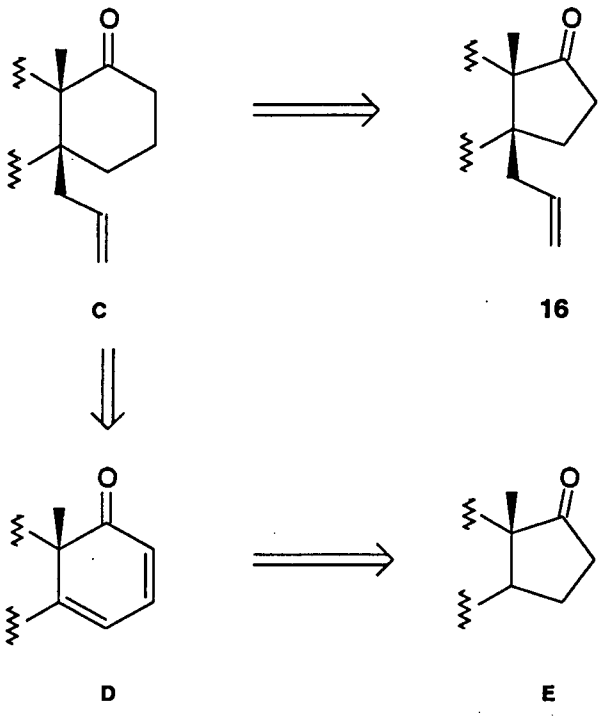
In the light of previous findings, a retrosynthetic analysis of the target molecule suggests again that intramolecular reductive coupling should be feasible and, in turn, that the necessary precursor could be derived from regioselective functionalisation of the 14β-allyl derivative of 17a-homoestrone (Scheme 5.1). It was further recognised that, in principle, the 14α-epimer would be equally effective, since the relative relationship of the prospective centres for intramolecular coupling are identical for either epimer. Accordingly, the problem would reduce to an efficient stereoselective synthesis of 14β- or 14α-allyl 17a-homoestrone. For the purpose of illustration, only the 14β-allyl precursor is further discussed.

Scheme 5.1



A stereodefined route to this precursor is obviously available via ring expansion of the available 14β-allylestrone (**18**), but an alternative, and conceptually-reversed, option could be considered in which the 14-allyl group is introduced into a preformed D-homoestrone derivative (Scheme 5.2). One such approach would be to achieve regioselective 1,6-allylation of a 17a-homo dienone. This is speculative, since we have not discovered any precedent for direct 1,6-alkylation of linear cyclohexadienones. However, an alternative strategy involving initial 1,4-allylation followed by [3,3] sigmatropic rearrangement would achieve the same result. Accordingly, 3-methoxy-17a-homoestra-1,3,5(10),14,16-pentaen-17a-one constituted an additional intermediate target which, in theory, could be accessed via ring expansion of estrone or via modification of earlier ring D precursors, available from total synthesis.

Scheme 5.2

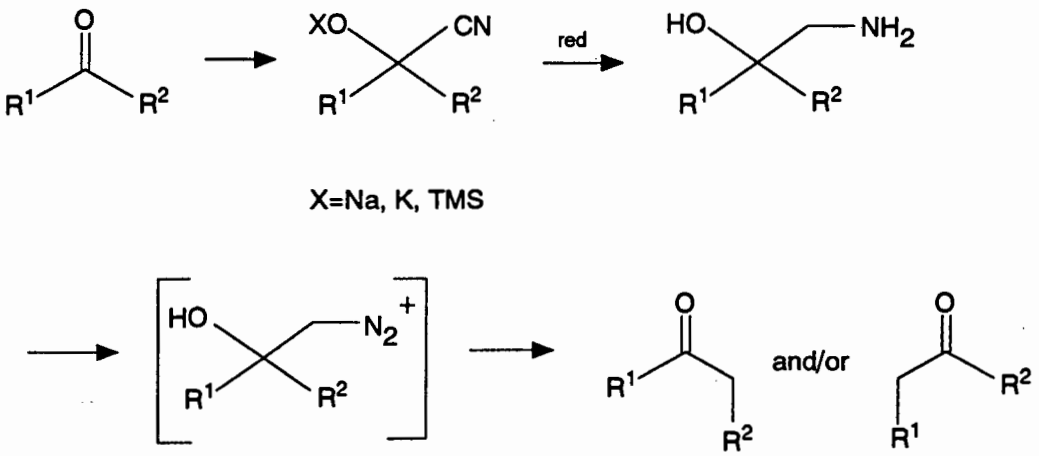


Much has been written on the topic of the one-carbon homologation of carbocycles.[88-92] The following overview of certain categories of ring expansion reactions is only intended to highlight key aspects of this large area of synthetic organic chemistry which pertain directly to the work undertaken for this thesis.

One of the major classes of one-carbon ring expansion reactions is broadly described by a pinacol-type rearrangement. The Tiffeneau-Demjanov expansion of cyclic

ketones falls into this category. This reaction involves the rearrangement of a diazonium ion formed by diazotisation of the corresponding amino alcohol. The amino alcohol is obtained from the ketone by reduction of the cyanohydrin or trimethylsilyl cyanohydrin (Scheme 5.3).[90] The rearrangement takes place under stereoelectronic control, with the bond antiperiplanar to the diaza leaving group migrating. In general though, unsymmetrical ketones often yield mixtures of regioisomeric homologation products, the rearrangement of the more substituted side being preferred.[89]

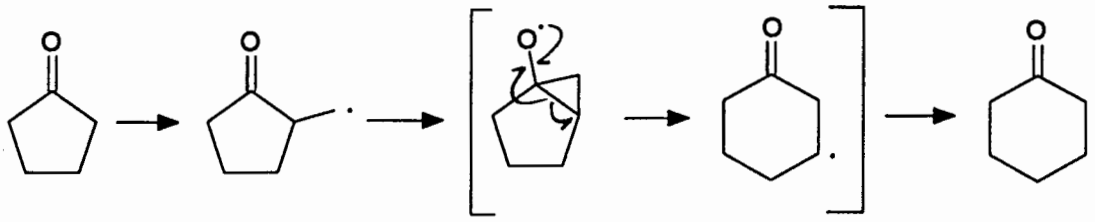
Scheme 5.3



Other variations for ketone homologations involve the use of diazoalkanes, especially diazomethane and ethyl diazoacetate, except that diazoalkanes have diminished reactivity towards cyclopentanones.[90] Use of both of these reagents also suffers from side-reactions, most notably the formation of spirooxiranes when the intermediate betaine collapses without migration occurring.

Another class of one-carbon insertion reactions involves the cleavage of the zero bridge of bicyclo[n.1.0] systems. Depending on the nature and environment of this central bond, a large variety of methods are known for the transformation of the bicyclic intermediate into the homologated carbocycle. These include acid-, base- and thermally-mediated rearrangements[93], and hydrogenolysis[94] among others. An extension of this concept involves ring expansions via carbene or radical intermediates. The mechanism of this type of reaction appears to proceed via formation of a primary methyl radical α to the carbonyl group, followed by attack on the carbonyl group, and subsequent cleavage of the internal bond of the cyclopropane moiety to form the ring expanded product.[95,96] (Scheme 5.4). This approach allows for regioselective ring homologation.

Scheme 5.4

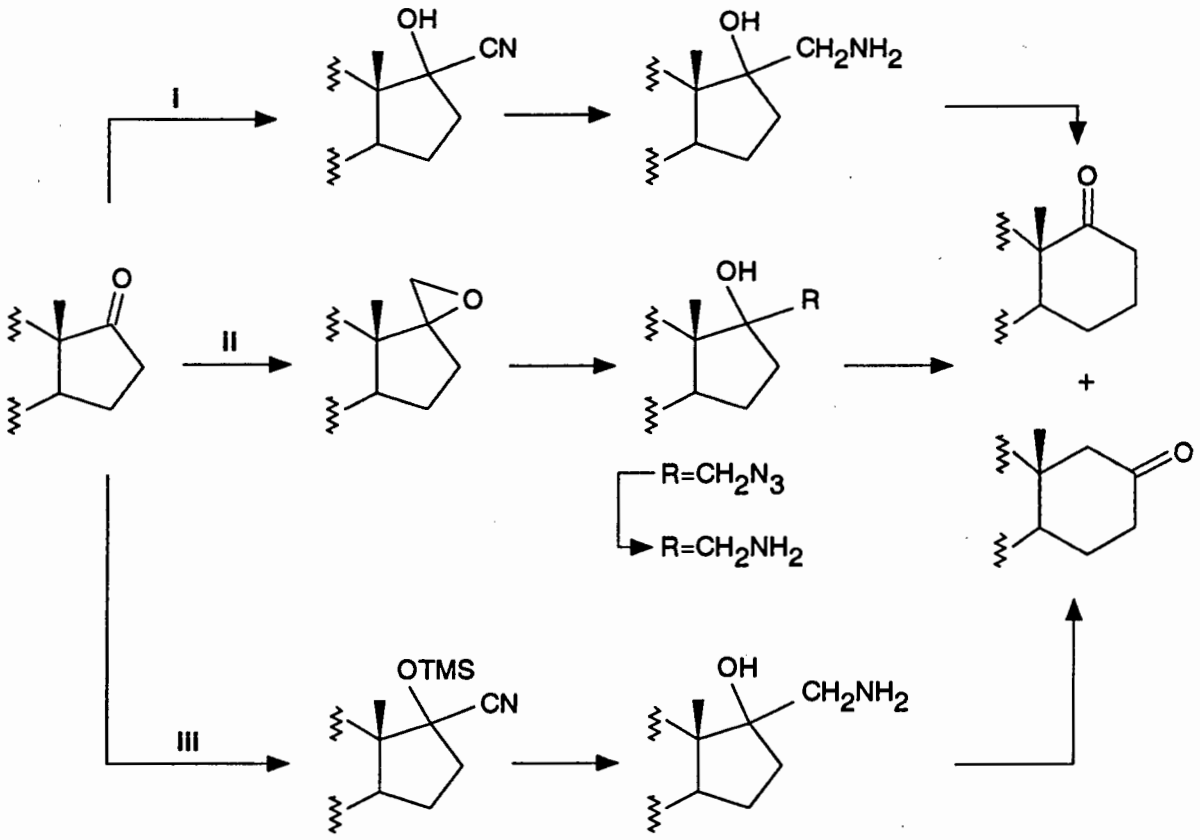


The short overview that follows, highlights some of the approaches towards ring D homologation of estrones or androstanes found in the steroid literature, and discusses some of the difficulties encountered, including unfavourable regioselectivity of expansion, lack of reactivity, and the associated low yields.

As early as the 1940's, Goldberg and Studer[97] used the Tiffeneau-Demjanov reaction to synthesise 17a-homoestrone. The initial step was conversion of estrone to its cyanohydrin with potassium cyanide, a reversible reaction with an inefficient equilibrium constant,[98] resulting in a low yield (*ca* 50%). The following step, reduction of the cyanohydrin to the methylamino alcohol with platinum oxide as catalyst, was also mediocre in yield. The reaction was non-reproducible owing to catalyst poisoning by traces of cyanide.[98] Lithium aluminium hydride could be used for this reduction, but the product becomes trapped in an insoluble aluminium-complex, leading again to lowered yields. The ring expansion step led to a mixture of 17a-homo regioisomers in an 8:1 ratio, favouring the 17a-ketone, but the overall yield for this step was low again (*ca* 20%) (Scheme 5.5, **i**).

Kirk and co-workers[99] prepared a number of 17a-homo-5α-androstane derivatives using similar Tiffeneau-Demjanov methodology and employing nitrous acid in the rearrangement step to give the D-homo-17a-ketone and a small amount of the regioisomeric 17-ketone (20:1 ratio) in *ca* 30% overall yield. An improvement in this Tiffeneau-Demjanov sequence was reported by Kirk and Wilson,[89] in which the 17-ketone of 3β-hydroxy-androst-5-en-17-one was converted almost quantitatively into the epimeric spirooxiranes by treatment with the trimethylsulfonium ylide. Conversion of the spirooxiranes into the hydroxy azides, followed by reduction with chromium(III) chloride or zinc dust, and rearrangement with nitrous acid, gave a mixture of the 17a-oxo and 17-oxo D-homo regioisomers (6:1 ratio) in high (*ca* 80%) overall yield (Scheme 5.5, **ii**).

Scheme 5.5

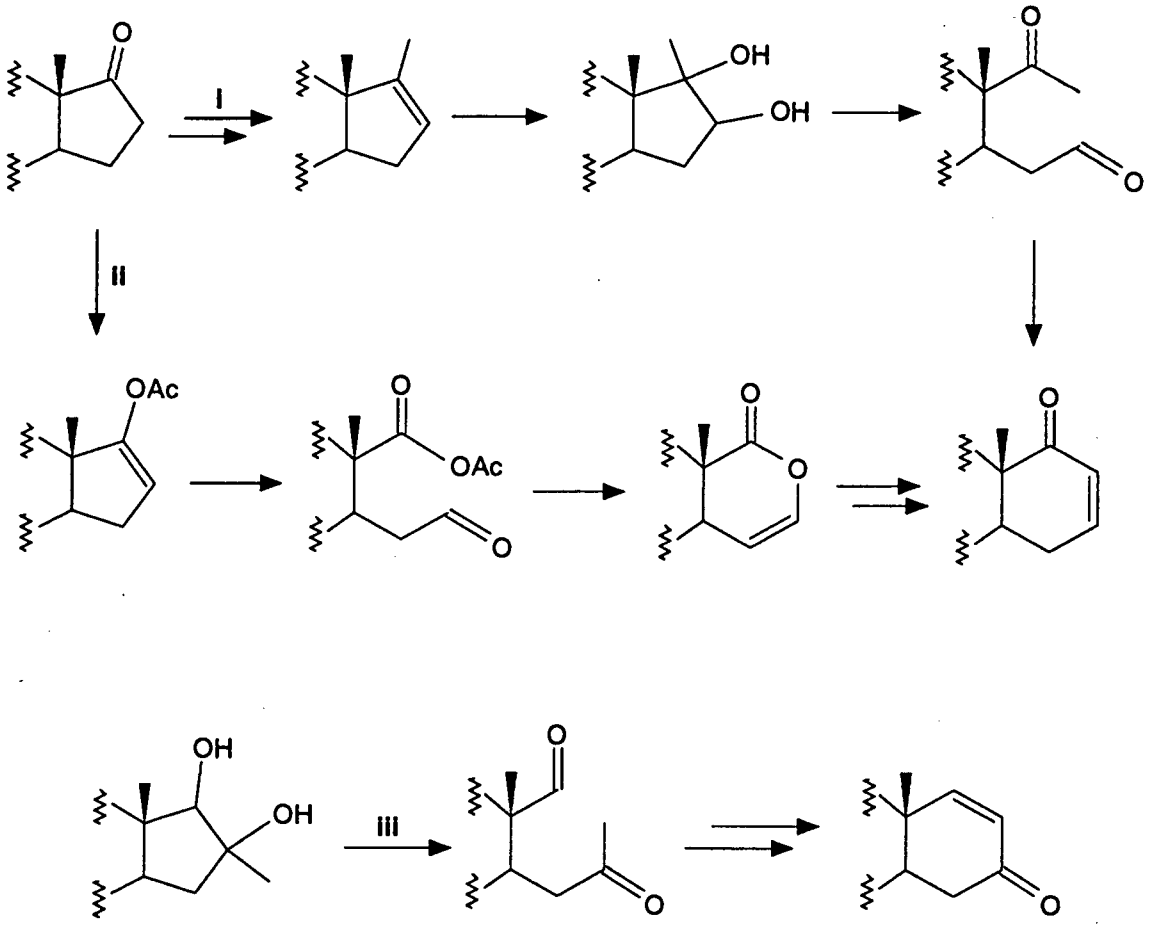


Evans[100], Steinberg[101], and Haffer[102] all used similar spirooxirane-hydroxy azide approaches with general success for ring D and ring C expansions. One of the problems encountered in this sequence, however, was the difficulty in forming the spirooxirane intermediate. Evans[100] mentioned that incomplete reactions were unavoidable with certain substrates. Kirk[103] described a similar problem when attempting to ring expand photo-isomerised 13α-androstane. Neither the 17-spirooxirane nor the conventional Tiffeneau-Demjanov 17-aminomethyl 17-hydroxy intermediate could be formed. This low reactivity was blamed on the *cis*-fusion of the ring D 17-ketones. In a more recent example of the Tiffeneau-Demjanov expansion sequence, Avery[104] used trimethylsilyl cyanide to convert 7α-methyl-3-methoxy-estra-1,3,5(10)-trien-17-one into its cyanohydrin. The trimethylsilyl cyanide is a less hazardous source of cyanide, and, because the reaction is no longer reversible, allows for better yields than when using KCN or NaCN. Conventional reduction and ring expansion gave the D-homo regioisomers in a 7:1 ratio, with the desired isomer being formed in 52% overall yield (Scheme 5.5, **iii**).

Another approach to 17a-homo steroid synthesis highlighted in the literature involves oxidative cleavage of ring D, followed by aldol closure of the resultant 16,17-seco-steroid.

Johns[105] used this approach, converting 3-methoxy-17-methyl-estra-1,3,5(10),16-tetraene into the *cis*-glycol by osmium(IV) oxide hydroxylation. The diol was cleaved in 80% yield to the 16,17-seco compound, which underwent aldol closure and dehydration to yield the 17a-homo enone in 40% yield for the last two steps (Scheme 5.6, **i**). The starting Δ^{16}-17-methyl compound, however, was isolated as one of the minor components of a retropinacol rearrangement of estradiol, and this was thus not a synthetically-viable route. Tyner[106] used an analogous approach, synthesising the 16-methyl-16,17-diol derivative of estrone 3-methyl ether, and employing an oxidative cleavage-aldol condensation sequence to give the Δ^{17}-17a-homo-16-ketone (Scheme 5.6, **ii**). Nickolson[107] made the 17a-homo enone by enol acetylation of estrone, oxidative cleavage of the Δ^{16}-bond, lactonisation, methylation-enol lactonisation, and aldol closure of the seco-steroid (Scheme 5.6, **iii**).

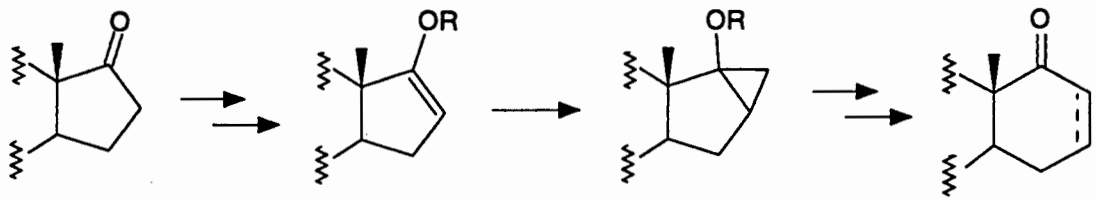
Scheme 5.6



It seemed possible, therefore, to find a more efficient conversion of estrone or the allyl ketone (**18**) to its Δ^{16}-17-methyl derivative for oxidative cleavage and intramolecular aldol condensation of the 16,17-seco-steroid to the desired 17a-homo compound.

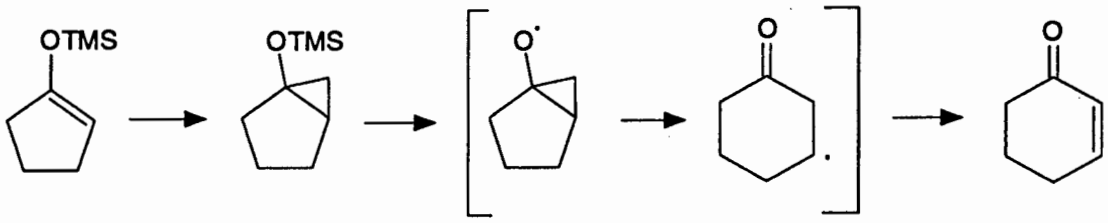
A third approach for the expansion of ring D was described by Johns and Salamon[108] and involved the addition of carbenes to ring D enol ethers and enol acetates. Subsequent cleavage of the zero bridge of the bicyclo[3.1.0] hexanoid moiety gave rise to the 17a-homo-17a-ketones or their Δ^{16}- derivatives in moderate (45-76%) yields (Scheme 5.7)

Scheme 5.7



We hoped to exploit this concept and improve upon the overall conversion by employing a recently developed method involving cyclopropanation of a silyl enol ether derivative followed by regioselective radical-mediated opening of the internal bond using iron(III) chloride in dimethylformamide (Scheme 5.8).[95]

Scheme 5.8



There is a considerable amount of literature on cyclopropanation of olefins covering a wide variety of cyclopropanation agents.[109] For the purpose of this study, we concentrated on the use of the Simmons-Smith reagents, *viz.* diiodomethane and an activated zinc species to generate the carbene source.[110] Diazomethane, polyhalomethanes, and halomethyllithiums are among other reported carbene sources,

but the Simmons-Smith intermediates have more controlled reactivity in general, demonstrating reduced side reactions.[109]

The original Simmons-Smith reagent was made using diiodomethane and a zinc-copper couple. An improvement involving the use of a zinc-silver couple seemed more appropriate for our system in that it has been used successfully for the cyclopropanation of cycloalkenyl silyl enol ethers,[111] and in the steroid field.[112] It has also been reported that sonication[113] and the presence of oxygen[114] accelerate the reaction. One of the most important improvements in cyclopropanations was the modification proposed by Furukawa[115] involving the use of diethyl zinc with diiodomethane (CH_2I_2). Advantages[116] of this procedure over other organozinc reagents include rapid formation of the reagent under mild conditions, compatibility with a broader range of substrates (including silyl enol ethers[117] and steroids[118]), and the use of non-coordinating solvents if desired. Another variation reported in the literature was the use of trialkylaluminiums with CH_2I_2 as a cyclopropanation reagent.[119] All of these methods demonstrated an enormous solvent dependance in order to achieve reproducibility and high yields.

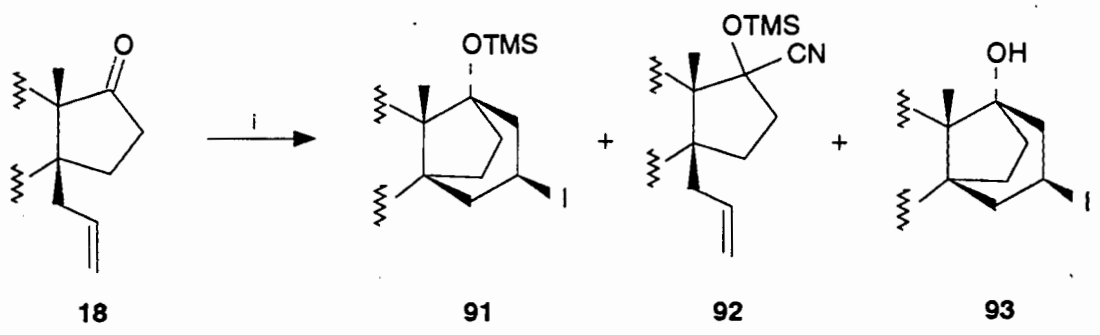
5.2 Attempts to Homologate Ring D of 14-Allyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (18)

Tiffeneau-Demjanov Approach. The ease of addition of a nucleophilic species to the 17-oxo group of the 14β-allyl 17-ketone (**18**) was uncertain in view of the additional steric factor provided by the 14β-allyl group. Tiffeneau-Demjanov cyanation of the allyl ketone (**18**) was thus first attempted using trimethylsilyl cyanide (TMSCN) as the cyanation agent, since it was expected to be more effective with respect to hindered ketones[120] and would not suffer from the equilibration problems associated with NaCN or KCN. Treatment of a dichloromethane solution of the allyl ketone (**18**) with TMSCN and zinc(II) iodide at 20°C for 3 h, gave rise to a mulitcomponent mixture (Scheme 5.9).

One of the minor products (10% yield) appeared to be an inseparable epimeric mixture (2:1 ratio, from NMR) of the 17-trimethylsilyloxy 17-cyanohydrins (**92a + 92b**). The trimethylsilyl group resonated as a nine-proton singlet at δ 0.25 (minor) and δ 0.29 (major). The infrared spectrum showed a weak nitrile absorption band at ν_{max} 2228 cm^{-1}, and the molecular ion of m/z 423 confirmed the structure.

Two other products, which comprised the bulk of the reaction mixture, were identified from spectral data as (17^2*S*)-17^2-iodo-3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17α-ol (**93**) (26%) and the 17α-OTMS derivative (**91**) (60%). The infrared spectrum of **93** indicated an OH absorption band at ν_{max} 3591 cm^{-1}, and the mass spectra of both compounds confirmed the presence of iodine (M-127 fragment).

Scheme 5.9



18 **91** **92** **93**

i, TMSCN, ZnI_2

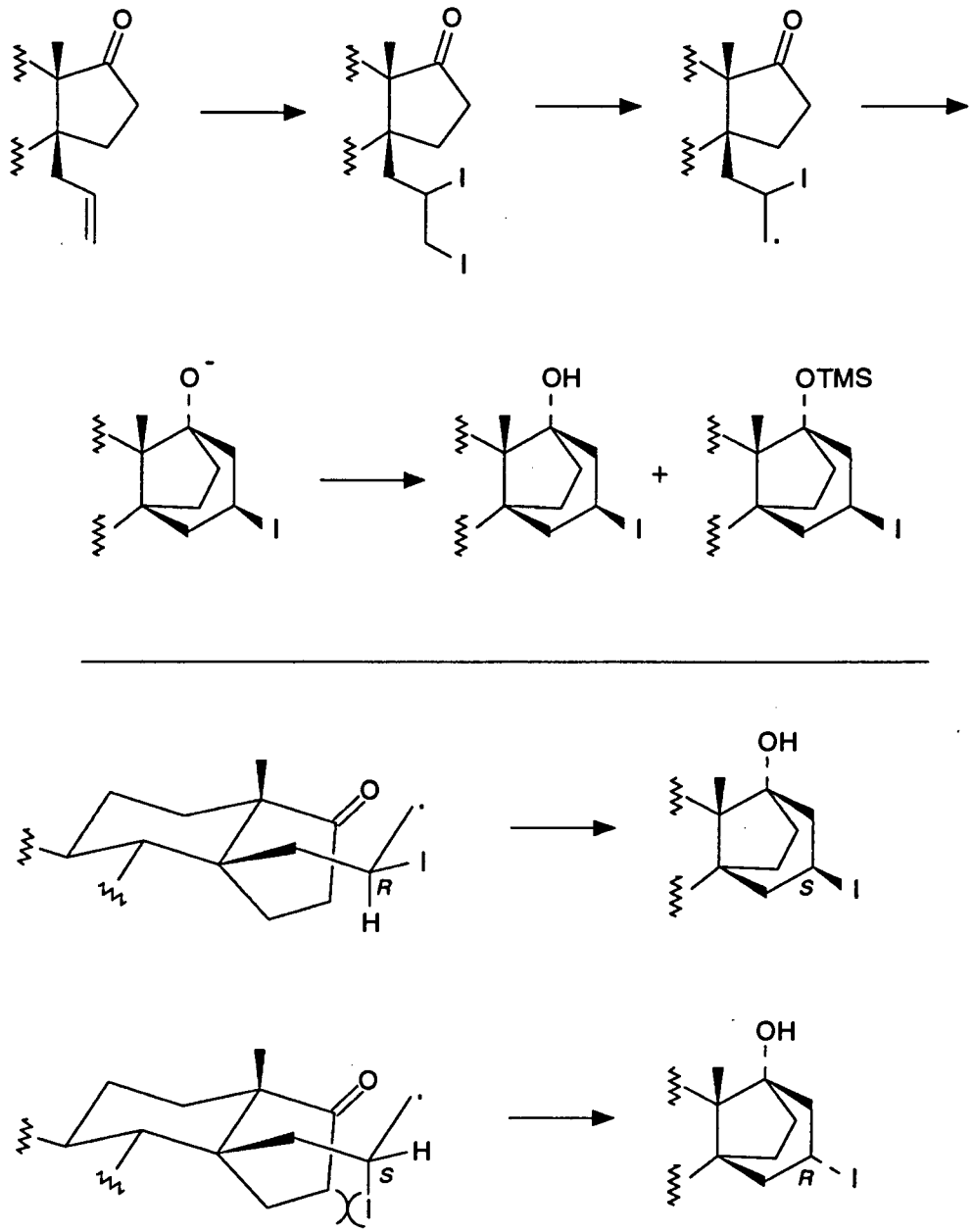
The NMR features of these two compounds, specified here for **93**, were similar, with 17^2-H_R resonating at δ 4.8 (tt, *J* 2 x 12 and 2 x 7 Hz). Crosspeaks in the COSY spectrum between this signal and four others located the 17^1- and 17^3-epimeric protons at δ 1.96 (t, *J* 2 x 12 Hz, 17^3-H_S), δ 2.17 (dd, *J* 12 and 7 Hz, 17^1-H_S), δ 2.27 (dd, *J* 12 and 7 Hz, 17^3-H_R) and δ 2.58 (t, *J* 2 x 12 Hz, 17^1-H_R).

The spectrum described above showed remarkable similarities to that of the 14β,17β-propano 17α,17^2-diol (**26**). The stereochemistry of **91** and **93** was assigned on the same basis as that for **26**. From models, the signal at δ 4.8 (tt, *J* 2 x 12 and 2 x 7 Hz) can only be accomodated by an *S*-configuration at C(17^2). The two large vicinal couplings to 17^1-H_R and 17^3-H_S are in agreement with the antiperiplanar relationship between these protons, while the smaller vicinal couplings to 17^1-H_S and 17^3-H_R are consistent with relative synclinal orientations.

The major reaction thus appears to involve addition of iodine to the 14β-allyl group, followed by attack of the terminal (14^3-) position on the 17-ketone, and quenching of the 17-O anion by either H^+ or TMS^+ (Scheme 5.10). CdI_2 is known to iodonate double bonds,[121] and since zinc and cadmium are in the same transition metal group, they are expected to possess similar reactivities. Once the iodination had taken place, it would be a simple matter to generate the primary (14^3-) radical (eg. hv) given the instability of *vic*-diiodides.[121] Iodocarbonyls are also known to be 'excellent substrates for atom transfer cyclisation'.[122] This intramolecular coupling reaction was not anticipated from the literature dealing with this method of cyanation, in which various substrates required varying amounts of ZnI_2 (0.03 - 0.23 equiv.) as catalyst for the reaction to be effective.[120] However, if less than 0.8 equivalents of ZnI_2 was used with the allyl ketone (**18**) as substrate, it was found that the reaction did not go to completion. When 0.8 equivalents was used, though, the competing iodination reaction dominated over the desired cyanation. The steric factors associated with the 17-oxo group of the

allyl ketone did not facilitate cyanation compared with the competing rapid iodination-intramolecular closure side-reaction.

Scheme 5.10



It can be clearly seen from a perspective view (Scheme 5.10) that the transition state requires an *R*-configuration at C(14^2), giving rise to *S*-configuration at C(17^2) in the cyclised product. Unfavourable interactions would prevent a reversal of the transition state configuration.

In an attempt to ascertain if this 14β-alkyl group participation reaction could be avoided by initially modifying the allyl group, the allyl ketone (**18**) was hydrogenated. It was reasoned that if the resultant 14β-propyl 17-ketone could be successfully cyanated at C(17), then prior regioselective functionalisation of the allyl bond in the allyl ketone could lead to a substrate more suited to the TMSCN/ZnI_2 reaction conditions. Catalytic palladium-mediated hydrogenation of an ethyl acetate solution of the allyl ketone (**18**) at 20° for 3 h gave the expected 14β-propyl 17-ketone (**94**) (87%). All spectroscopic and analytical data were consistent with the structure.

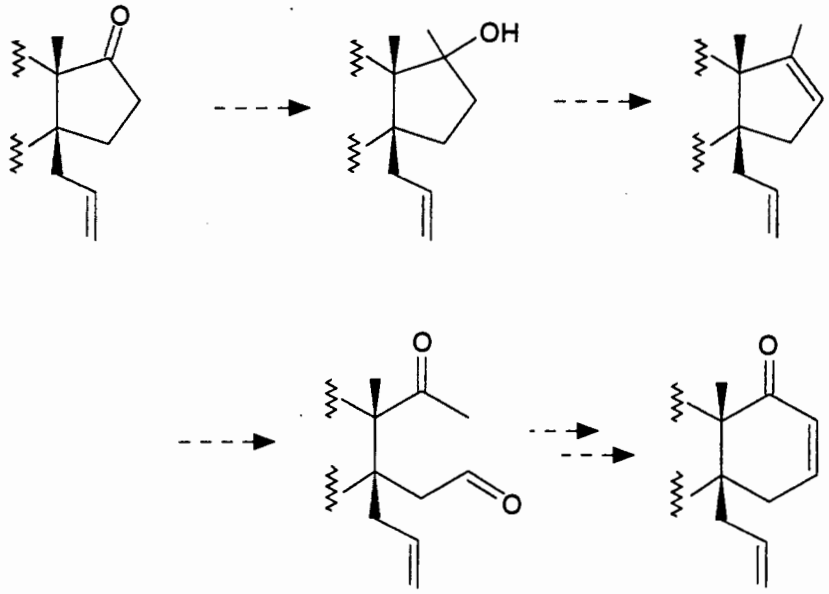
Reaction of this 14β-propyl 17-ketone (**94**) with TMSCN and ZnI_2 in a similar manner to that described above, however, resulted in a multicomponent mixture. It appears, therefore, that the side-rections are not only limited to areas of unsaturation.

Owing to the lack of success in cyanation of the allyl ketone (**18**), attempts were made to form the 17-spirooxirane by exposing the allyl ketone to the trimethylsulfonium ylide (generated by the sodium hydride treatment of trimethylsulfonium iodide)[123] for 4 h at 20°C and 16 h at 60°C. Only starting material was recovered, however. This lack of reactivity of the *cis*-fused allyl ketone was in agreement with the findings of Evans[100] and Kirk[103], and corroborates the suspicion that the 14β-allyl group is a severely inhibiting factor in nucleophilic attack at C(17).[55]

Seco-Steroid Approach. The failure of the allyl ketone to form an intermediate suited to Tiffeneau-Demjanov ring expansion prompted an investigation of another approach to a ring-expanded product, *viz.* oxidative cleavage of a Δ^{16}-17-methyl derivative, followed by aldol condensation of the seco-steroid. Methylation of 17-oxo group of (**18**), followed by dehydration to form the Δ^{16}-17-methyl compound was expected to provide a substrate for oxidative cleavage and subsequent aldol condensation (Scheme 5.11).

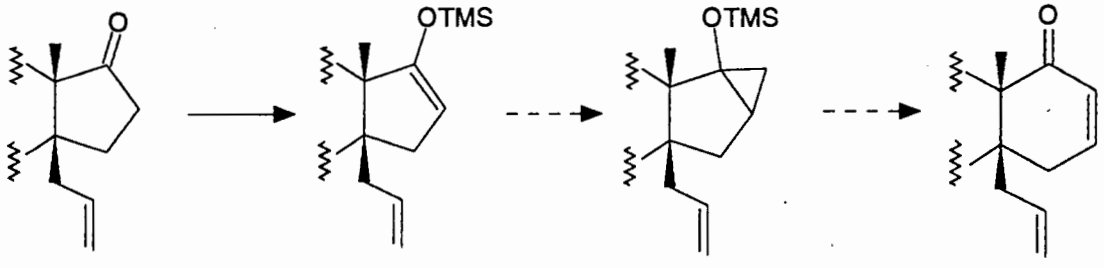
The allyl ketone (**18**) failed to react with methylmagnesium iodide under a variety of conditions (solvent and temperature). Use of methyllithium, over a range of temperatures (-78°C to reflux) was equally ineffective. In all cases, only allyl ketone was recovered. This failure to react is consistent with the attempted cyanation, and could again be attributed to steric factors. Alternatively, it is also possible that enolisation of the sterically-hindered ketone under Grignard conditions was intervening. This enolisation is a well-recognised problem,[124] but can be supressed by the use of different reaction conditions, such as non-hydroxylic, aprotic solvents and an alkyllithium at very low temperatures. However, in view of the outcome of an analogous reaction on estrone 3-methyl ether (*cf.* section 5.4), it was decided to abandon this approach.

Scheme 5.11



Cyclopropanation-Cleavage Approach. The next attempt at homologation of ring D involved cyclopropanation of the silyl enol ether, followed by regioselective cleavage of the 16,17-bond of the derived 16,17-methylene compound (Scheme 5.12).

Scheme 5.12



95

Treatment of the allyl ketone (**18**) with lithium diisopropylamide at -78°C for 45 min, followed by trapping of the enolate anion with chlorotrimethylsilane gave rise to a single, unstable product, formulated as the silyl enol ether (**95**). The instability of the compound precluded full characterisation, but a diagnostic infrared absorption band at ν_{max} 1638 cm^{-1} (C=C), and a molecular ion of m/z 396 confirmed the structure. The 17-OTMS protons resonated at δ 0.22 as a nine-proton singlet in the NMR spectrum, and a signal at δ 4.34 (dd, *J* 2.9 and 1.7 Hz) was assigned to 16-H.

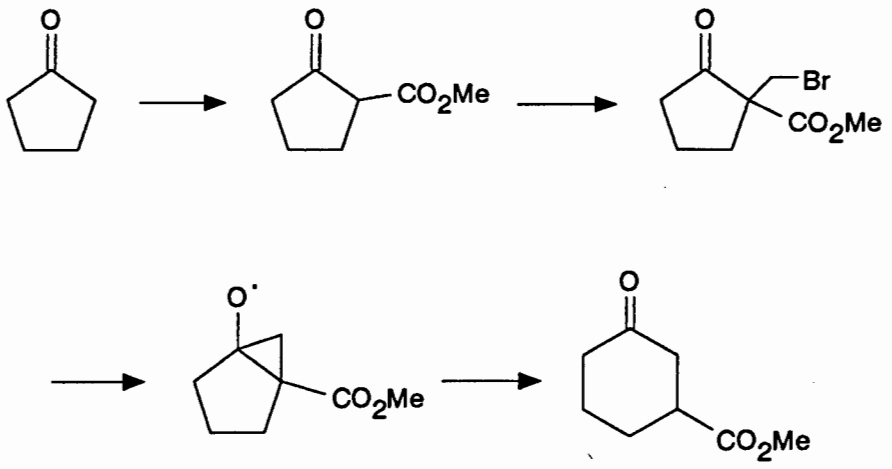
The instability of the silyl enol ether required that the material be used immediately after preparation. Initial attempts at cyclopropanation of the silyl enol ether (**95**) using the conventional Simmons-Smith reagent (CH_2I_2 and Zn-Cu) under a variety of conditions were completely unsuccessful, leading to hydrolysis of **95** and recovery of the allyl ketone (**18**) in all cases. The variations applied include the use of diethyl ether or tetrahydrofuran as solvent, the use of a range of temperatures (0°C to reflux), and the use of the purported improvements involving ultrasound and the presence of oxygen. Equally unsuccessful was the CH_2I_2/Zn-Ag reagent. Even diethyl zinc could not promote cyclopropanation. Because of the solvent dependency of this reagent, a number of solvents used successfully by others were employed, including tetrahydrofuran, n-butyl ether, benzene, toluene, dioxane, 1,2-dichloroethane, and 1,2-dimethoxyethane. The procedure exploiting CH_2I_2 and triethylaluminium was also attempted using a range of temperatures and variety of solvents (n-butyl ether, benzene, toluene, 1,2-dichloroethane, and 1,2-dimethoxyethane) with similar lack of success. Another reported conversion of ketones to cyclopropanols[125] involving treatment of the allyl ketone (**18**) with lithium diisopropylamide (LDA), then adding CH_2I_2 and samarium(II) iodide sequentially to the enolate, again only led to recovery of starting material. This inability to form the 16,17-methylene compound was a further indication of the poor ring D reactivity of the 14β-allyl 17-ketone (**18**).

Another variation involved the attempted synthesis of the enol acetate or enol benzoate of **18** in the hope that these substrates would be more amenable to cyclopropanation.[109] However, attempts at enol acetylation (refluxing acetic anhydride and isopropenyl acetate catalysed by *p*-TsOH) or enol benzoylation (LDA generation of enolate, then trapping with benzoyl bromide) of **18** were unsatisfactory, leading to multicomponent mixtures.

The lack of reactivity of the allyl ketone (**18**) and derived silyl enol ether (**95**) forced us to abandon this approach.

Radical-Mediated Ring Expansion. Dowd and co-workers[96] have described a ring expansion procedure in which a β-keto ester is alkylated with a methylene dihalide, and the resultant haloalkyl β-keto ester derivative is subjected to a radical-mediated rearrangement (Scheme 5.13). The ester plays a critical role by providing activation for the halomethylenation as well as activating the ketone towards attack by the methylene radical and providing the driving force for cyclopropane ring cleavage. The radical intermediate is similar to that shown for the expansion of the cyclopropyl silyl enol ether, and an attempt was made to apply this method to the allyl ketone (**18**).

Scheme 5.13

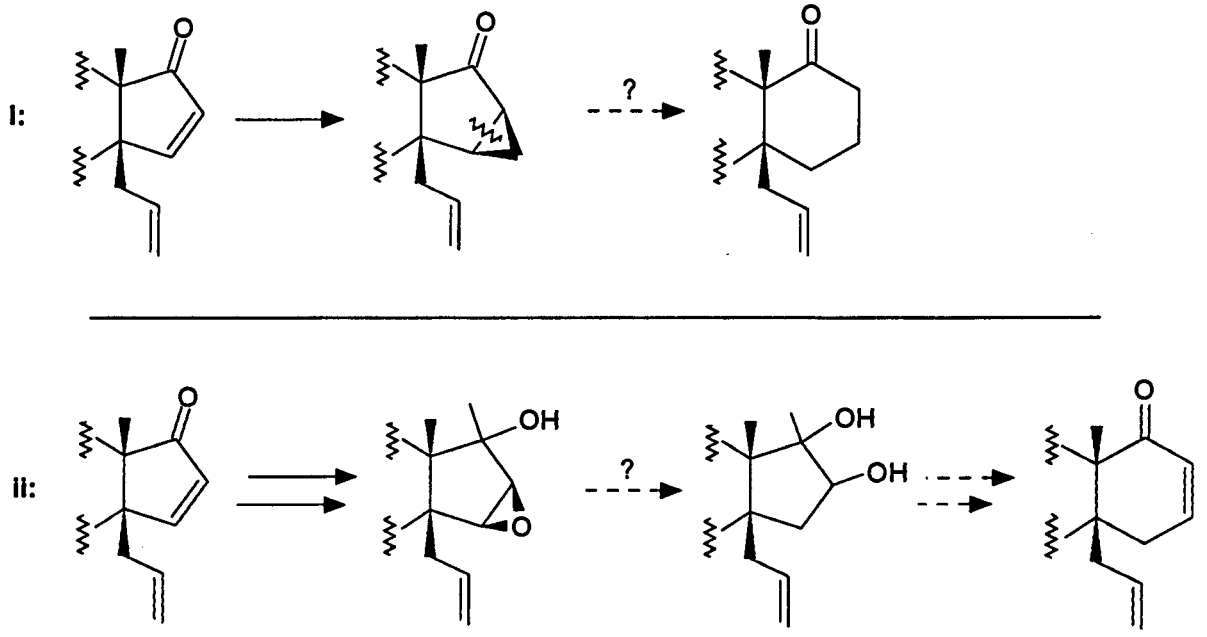


Treatment of the allyl ketone (**18**) with sodium hydride and dimethyl carbonate, even for prolonged peroids and at elevated temperatures were completely without success. In an attempt to evaluate the α-reactivity of the allyl ketone, **18** was subjected to conventional α-bromination conditions ($CuBr_2$, methanol-benzene, reflux). Again, only starting material was recovered. Enolisation of the ketone with LDA followed by attempted alkylation with methyl iodide or methylene bromide were also met with frustration. This approach was thus abandoned in view of the fact that, even if the α-alkylation had been successful, the product would contain a γ-removed ester, which may have been problematical to remove.

5.3 Attempted Homologation of Ring D of 14-Allyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (17)

Having ascertained the unsuitability of the 14β-allyl 17-ketone (**18**) as a ring expansion substrate, the 14β-allyl Δ^{15}-17-ketone (**17**) appeared to be the next most appropriate starting material for ring expansion, if the Δ^{15}-unsaturation could be exploited for one-carbon insertion into ring D. Two approaches were envisaged: a) 15,16-cyclopropanation of the enone, followed by regioselective cleavage of the 15,16-bond (Scheme 5.14, **i**); or b) epoxidation of the Δ^{15}-bond, methylation at C(17), and regioselective hydride attack of the epoxide giving rise to a 16,17-diol, which could undergo oxidative cleavage followed by aldol closure of the seco-steroid (Scheme 5.14, **ii**).

Scheme 5.14

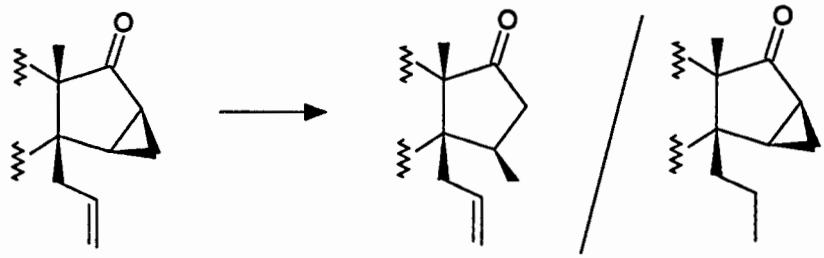


Cyclopropanation Approach. The trimethyloxosulfonium ylide is known to cyclopropanate α,β-unsaturated ketones.[126,127] The ylide is formed *in situ* by base (eg. NaH) treatment of trimethylsulfoxonium iodide in dimethylformamide (DMF) prior to addition of the substrate. The mechanism involves 1,4-addition of the carbon nucleophile, followed by intramolecular substitution of the carbanionic α-carbon, expelling the sulfide moiety from the betaine.[128] This reaction is usually stereoselective.[127]

Applying this methodology to the allyl enone (**17**) gave rise to the 15β,16β-cyclopropyl derivative (**96**) in 85% yield. A relatively low-frequency carbonyl absorption band at 1705 cm^{-1} in the infrared spectrum of **96** was within the range expected for cyclopropyl ketones.[129] The NMR spectrum of **96** showed unresolved multiplets at δ 1.04 and 1.96 for the methylene protons of the cyclopropyl ring, and the survival of the allyl group was clear.

It was expected that metal-ammonia reduction of the cyclopropyl ketone (**96**) would cleave the 16-3' bond,[130] but it was hoped that hydrogenolysis would be more successful in cleaving the 15-16 bond (Scheme 5.15). Treatment of the cyclopropyl compound (**96**) with lithium in ammonia at -78°C for 10 min, gave the 15β-methyl 17-ketone (**97**) in 58% yield, accompanied by starting material. The structure of the product was evident from the signal for the secondary methyl group in the NMR spectrum. The 15β-methyl group resonated at δ 1.21 (d, *J* 6.5 Hz), while the 16-protons were assigned

Scheme 5.15



96 **97** **98**

to the signals at δ 2.57 (dd, *J* 14.9 and 7.8 Hz, 16β-H) and 2.73 (dd, *J* 14.9 and 9.3 Hz, 16α-H). The stereochemical assignments for 16-H_2 are based on models, which indicate that the 16α-H should have a larger vicinal coupling to 15α-H that the 16β-H. The magnitude of the Cotton effect for **97** (*viz.* +2.47) was consistent with the trend found for 15β-methyl substituted 14β-17-ketones,[131] thereby confirming that initial cyclopropanation had taken place on the β-face of the enone (**17**).

Hydrogenolysis of the cyclopropyl ketone (**96**) was attempted, based on the expectation that 'if the geometry of the reactant is such that one bond is more strained than the others, hydrogenolysis tends to occur at that bond'.[94] Cyclopropanes have been shown to undergo hydrogenolysis using palladium, platinum or nickel catalysts under *ca* 400 kPa hydrogen pressure, but the bond that is most accessible to the catalyst surface is the one that is usually cleaved.[132] This did not bode well for internal bond scission of **96**.

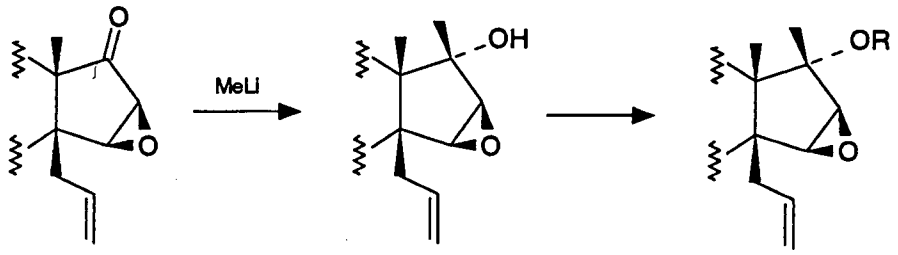
Hydrogenation (100 kPa H_2) of an ethanolic solution of the cyclopropyl compound (**96**) with palladium on carbon gave, after 6h, the 14β-propyl 15β,16β-cyclopropyl 17-ketone (**98**) in quantitative yield. This was evident from the disappearance of the allyl group multiplets, but retention of the cyclopropyl signals in the NMR spectrum of **98**. The carbonyl absorption band at 1705 cm^{-1} was still present in the infrared spectrum. More forcing conditions for hydrogenolysis were also employed, including reflux in acetic acid under hydrogen pressure with Pd-C catalysis, reflux in acetic acid under H_2 using Raney nickel (Aldrich, W2) as catalyst, and exposure to 2000 kPa H_2 pressure with equimolar Pd-C in ethanol. In all cases, the only product was that of hydrogenation of the 14β-allyl side-chain. Cleavage of the 15-16 bond is clearly not possible in this case, perhaps as a result of steric inaccessibility to the catalyst surface.

Epoxidation Approach. It is well-known that α,β-unsaturated ketones can be epoxidised chemoselectively with a nucleophile such as the peroxide anion.[127,133] Reaction of a methanolic solution of allyl enone (**17**) with NaOH-H_2O_2 at 0°C for 3 h resulted in clean, stereoselective epoxidation to give the 15β,16β-epoxy 17-ketone (**99**)

in good yield (Scheme 5.14, **ii**). The configurational assignment was based on the expectation that the β-face of the ring D enone is more exposed, as was ascertained in the cyclopropyl derivative (**96**). The 15α- and 16α-protons resonated as an AB multiplet at δ 3.48 and δ 3.73 (each d, *J* 2.4 Hz).

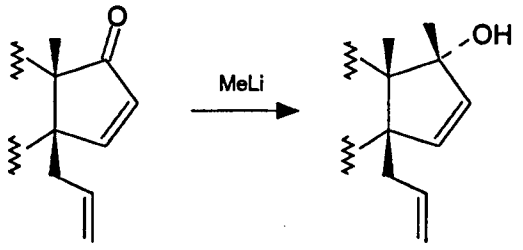
Methylation of the epoxy ketone (**99**) with methyllithium at -78°C gave a single product, assumed to be the 17β-methyl 17α-alcohol (**100**) (Scheme 5.16) on the expectation that methylation should proceed more readily on the more accessible β-face of the molecule.

Scheme 5.16



99 **100** **101**, R=Ac

102, R=TMS



17 **103**

The NMR spectrum of the non-crystalline epoxide (**100**) showed the expected AB multiplet for 15α- and 16α-H, and a methyl singlet at δ 1.41. In order to confirm the stereochemistry at C(17), and in an attempt to synthesise a crystalline derivative of **100**, the 17-acetate was synthesised under conventional conditions (acetic anhydride, pyridine, DMAP). The reaction was slow (72 h) owing to the tertiary nature of the hydroxy group, the yield was low (*ca* 20%), and the product (**101**) was also non-crystalline (Scheme 5.16). Treatment of the epoxy alcohol (**100**) with *bis*trimethylsilylacetamide[134] in DMF at 80°C for 75 h gave the 17-trimethylsilyloxy derivative (**102**) (44%), also a non-crystalline product (Scheme 5.16). The relevant data for **101** and **102** is tabulated in Table 5.17.

Table 5.17: NMR Data for Epoxy Acetate (**101**) and Silyloxy Epoxide (**102**)

	101 (R=Ac)	**102** (R=TMS)
15α-H	δ 3.46, d, *J* 2.6 Hz	δ 3.32, d, *J* 2.6 Hz
16α-H	δ 4.04, d, *J* 2.6 Hz	δ 3.44, d, *J* 2.6 Hz
17β-Me	δ 1.56, 3H, s	δ 1.41, 3H, s

The downfield shift of the 16α-proton in the acetate (**101**) may be due to the deshielding anisotropic influence of the acetoxy group on the α-face which is absent in the 17α-OTMS derivative (**102**), and supports the 17α-OR configuration of epoxy alcohol (**100**).

The epoxidation-methylation sequence described above was satisfactory, but an alternative pathway to the epoxy alcohol (**100**) was also investigated. Methylation of the allyl enone (**17**) with methyllithium at -78°C proceeded rapidly (1 h) to yield the non-crystalline Δ^{15}-alcohol (**103**) (85%), the structure of which was confirmed from spectroscopic data (Scheme 5.16). This result is in stark contrast to the lack of reactivity of the allyl ketone (**18**) towards methylation (*cf.* section 5.2). However, attempted Sharpless epoxidation of **103** using the conventional *tert*-butyl hydroperoxide – vanadyl acetoacetonate reagent was unsuccessful. This was undoubtedly due to the failure of the expected directing effect of the 17α-hydroxy group to overcome the steric hindrance to α-face addition.

Treatment of the epoxy alcohol (**100**) with lithium aluminium hydride in refluxing THF for 2 h was required to open the 15,16-epoxide. This yielded a multicomponent mixture, which was directly acetylated in order to facilitate separation and characterisation, to give a separable four-component mixture (**104**, **105**, **106**, and **107** in 32, 25, 5, and 20 % yield respectively). The diagnostic spectroscopic data for the four compounds (**104-107**) are tabulated below (Table 5.18).

The NMR features of compounds **104** and **105** clearly indicate the presence of a secondary methyl and two acetoxy groups. By contrast, product **106** must arise from a skeletal rearrangement since the molecular structure is unrelated to the other three products, and the allyl group signals are absent. Remote double bonds are known to participate in epoxide openings, sometimes involving skeletal rearrangements.[135] Compound **107** appears to have a structure consistent with a tertiary methyl and a secondary hydroxy group.

Table 5.18: Key Spectral and Analytical Data for Compounds **104**, **105**, **106** and **107**

	104	**105**	**106**	**107**
A[a]	1731	1736	1727	3602, 1724
B[b]	$C_{27}H_{36}O_5$	$C_{27}H_{36}O_5$	$C_{25}H_{32}O_2$	$C_{25}H_{34}O_2$
C[c]	δ 0.78 (3H, d, *J* 7.2 Hz)	δ 0.98 (3H, d, *J* 7.2 Hz)	δ 0.87 (3H, s)	δ 1.50 (3H, s)
	δ 2.05 (3H, s)	δ 2.01 (3H, s)	δ 2.08 (3H, s)	δ 2.02 (3H, s)
	δ 2.07 (3H, s)	δ 2.06 (3H, s)	-	-
	δ 5.73 (1H, dd, *J* 9.8 & 5 Hz)[d]	δ 5.0 (1H, dd, *J* 8.2 & 6.4 Hz)[d]	δ 4.2 (1H, t, *J* 2 x 3.2 Hz)	δ 1.8 (1H, dd, *J* 15 & 9 Hz)[d]
	δ 5.73 (1H, d, *J* 5 Hz)[d]	δ 5.62 (1H, d, *J* 8.2 Hz)[d]	δ 4.25 (1H, s)	δ 2.4 (1H, dd, *J* 15 & 9 Hz)[d]
			δ 5.00 (1H, s)	δ 5.65 (1H, t, *J* 2 x 9 Hz)[d]

[a] Absorption in IR spectrum as ν_{max}/cm^{-1}

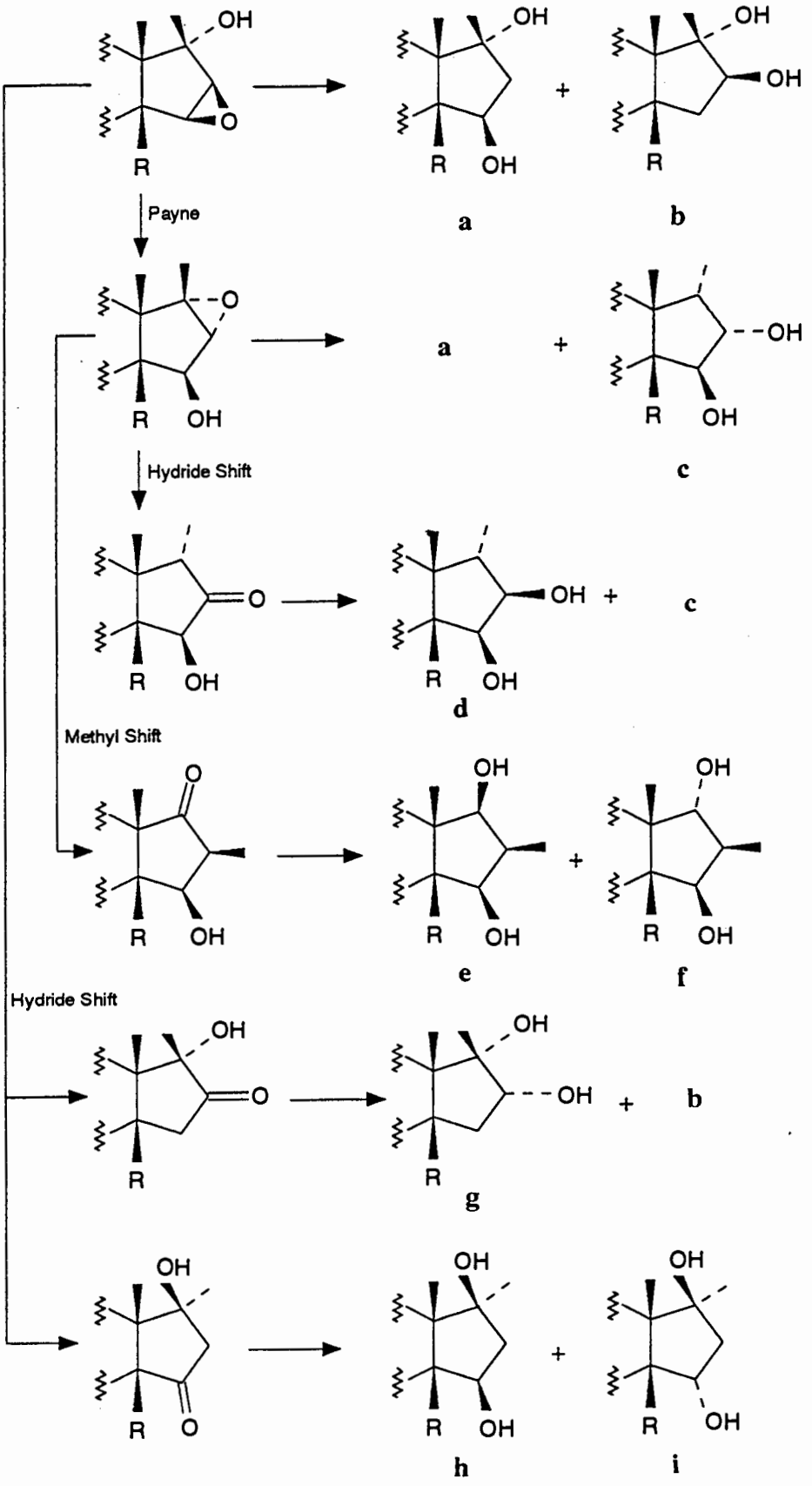
[b] Molecular formula determined from mass spectrum

[c] NMR data

[d] Coupled in COSY spectrum

The complexity of this reaction mixture clearly indicated that simple hydride opening of the epoxide could not be the only reaction pathway, since only two regioisomeric products would be expected. Additionally, the major products revealed the presence of secondary methyl groups, which indicates the intervention of rearrangements under the reaction conditions. Hydroxy groups which are β to the oxirane ring can readily participate in the opening of an epoxide if the geometrical features are favourable. This is known as the Payne rearrangement, and has been illustrated for many substrates including steroids.[136] The Payne rearrangement will not account for two secondary

Scheme 5.19



Notes: R=Allyl

Numbered compounds all arise from hydride attack of the relevant epoxide or ketone

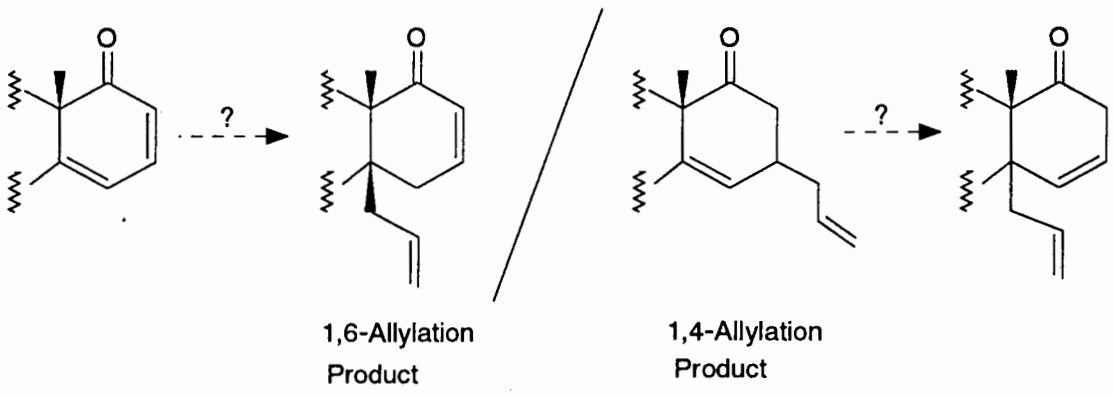
methyl groups, however. Additional hydride and methyl shifts must thus lead to further rearrangement products. Scheme 5.19 depicts the array of products which could be formed under the reaction conditions.

From the data in Table 5.18, it is evident that compounds (**104**) and (**105**) could have one of the structures represented by **c**, **d**, **e**, or **f**, and compound **107** may have the structure depicted for **a**, **b**, **g**, **h** or **i**, of which **b** was the desired product of epoxide opening. The fact that **107** was only formed in 20% yield, along with the complexity of the reaction outcome owing to competing rearrangements, forced us to abandon this route. This interesting problem warrants further attention, though, in view of analogous reduction of ring D epoxides by Bull and Sefton.[136]

5.4 3-Methoxy-17a-homoestra-1,3,5(10),14,16-pentaen-17a-one

In view of the failure of the exploratory approaches to ring expansion of both the allyl ketone (**18**) and the allyl enone (**17**), the alternative strategy to the target 14-allyl 17a-homo ketone was investigated. This approach involved initial ring expansion of estrone, followed by introduction of a 14-allyl group. 3-Methoxy-17a-homoestra-1,3,5(10),14,16-tetraen-17a-one was thus the primary target compound for an investigation into the scope for 1,6-conjugate addition of an allyl group to C(14) or tandem 1,4-addition of an allyl group followed by a sigmatropic rearrangement (Scheme 5.20).

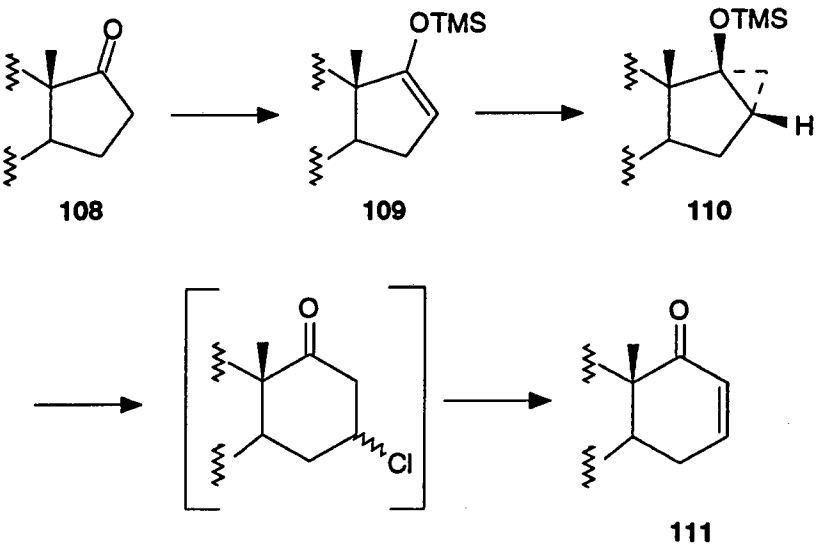
Scheme 5.20



5.4.1 3-Methoxy-17a-homoestra-1,3,5(10),16-tetraen-17a-one. Cyclopropanation of the trimethylsilyl enol ether of estrone (**109**) occurred readily (30 min) at 20°C using

CH_2I_2 and diethyl zinc in benzene. Other solvents (eg. THF, n-Butyl ether) were not effective; neither was the use of conventional Simmons-Smith conditions (Zn-Cu/ Zn-Ag) (Scheme 5.21).

Scheme 5.21



The trimethylsilyloxy cyclopropyl compound (**110**) was highly crystalline and stable. The 3'-cyclopropyl protons resonated as doublets of doublets at δ 0.74 (*J* 9 and 6.3 Hz, 3'-H_{exo}) and 1.01 (*J* 6.3 and 4 Hz, 3'-H_{endo}), while 16β-H was a complex multiplet at δ 0.87.

Iron(III) chloride is known to regioselectively ring expand this type of silyloxy cyclopropyl compound. The regiochemistry is believed to be due to the radical nature of the reaction, but it is unclear as to the exact mechanism, and as to whether a metal homoenolate is involved. The overall effect, however, is regioselective cleavage of the internal bond of the bicyclic moiety to form a β-chloro expanded ketone which, either spontaneously or with sodium acetate-methanol, eliminates HCl to yield the enone.[95]

Thus, slow addition of the cyclopropyl compound (**110**) in DMF-pyridine to iron(III) chloride in DMF proceeded smoothly. Isolation of a crude product mixture by work-up, and exposure of this residue to sodium acetate in refluxing methanol overnight, yielded the 17a-homo enone (**111**) in 76% overall yield from estrone (Scheme 5.21). This compound has been reported in the patent literature, but full spectral and analytical data was not available for comparison. Thus, a comprehensive spectroscopic analysis of **111** was performed; all data were consistent with the structure. Table 5.22 shows extensive assignments of the NMR spectrum.

Table 5.22: ^{1}N-NMR Assignments for 3-Methoxy-17a-homoestra-1,3,5(10),16-tetraen-17a-one (**111**)

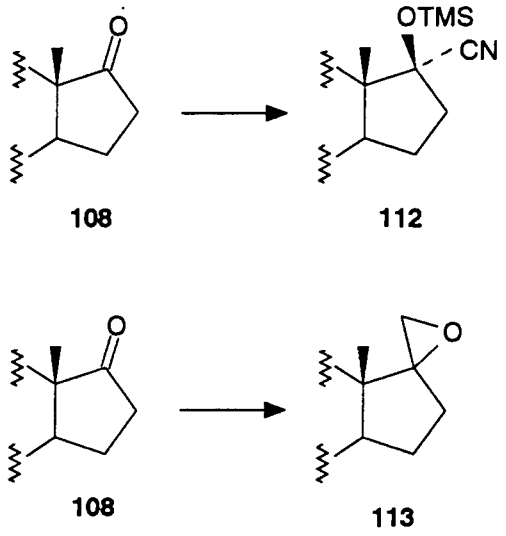
δ /ppm	Int.	Mult.	*J* /Hz	Assignment
1.04	3H	s		13β-Me
1.36	1H	m		12-H
1.78	1H	dt	10.9 & 2 x 4.5	14α-H
2.04	1H	m		15α-H
2.12	1H	dt	13.8 & 2 x 3.2	12-H
2.26	1H	td	2 x 10.9 & 3.8	9α-H
2.38	1H	dq	13.3 & 3 x 3.6	11α-H
2.56	1H	dt	19.2 & 2 x 4.5	15β-H
2.86	2H	m		6-H_2
3.77	3H	s		3-OMe
5.95	1H	ddd	10.1, 3 & 1.1	17-H
6.62	1H	d	2.8	4-H
6.72	1H	dd	8.8 & 2.8	2-H
6.89	1H	ddd	10.1, 6 & 2.1	16-H
7.22	1H	d	8.8	1-H

The selectivity and ease of this method of ring expansion in this particular case was remarkable. Other, less successful, attempts at synthesising the 17a-homo enone are briefly mentioned below.

Tiffeneau-Demjanov Approach. In a brief investigation of the reactivity of estrone 3-methyl ether towards cyanation, treatment of estrone (**108**) with TMSCN and ZnI_2 in dichloromethane at 20°C for 3h gave the 17β-trimethylsilyloxy 17α-carbonitrile (**112**) in 84% yield (Scheme 5.23).

The spirooxirane derivative of estrone (**113**) was equally smoothly formed in the presence of the trimethylsulfonium ylide (Scheme 5.23).[123] The ease and selectivity of these transformations is in direct contrast to the inability of the allyl ketone (**18**) to undergo analogous reactions.

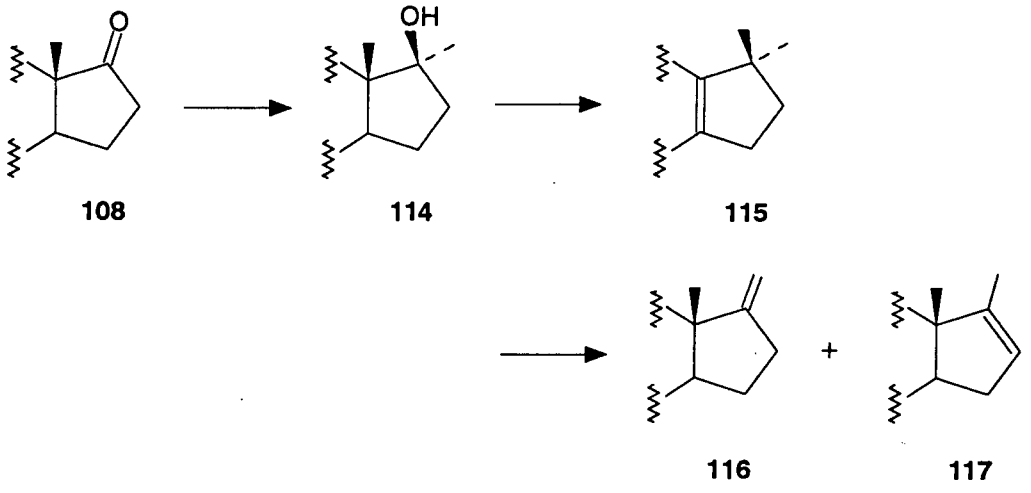
Scheme 5.23



Seco-Steroid Approach. Other approaches to the synthesis of the 17a-homo enone (**111**) were briefly examined and abandoned owing to poor regioselectivity during crucial steps.

In the first instance, conventional synthesis of a 17-methyl Δ^{16}-precursor for hydroxylation-oxidative cleavage was attempted. Grignard methylation of estrone (**108**) gave the expected 17α-methyl 17β-alcohol (**114**) (72%), acid treatment of which led to a complex mixture in which the major component appeared to be the predictable product of Wagner-Meerwein rearrangement (**115**) (Scheme 5.24).[137]

Scheme 5.24



More controlled dehydration of the methyl alcohol (**114**) with methyltriphenoxyphosphonium iodide or phosphorous oxychloride (with or without the presence of Hünig's base) led to similarly constituted inseparable mixtures of the exo- and endocyclic methylene compounds (**116** and **117**) (Scheme 5.24).

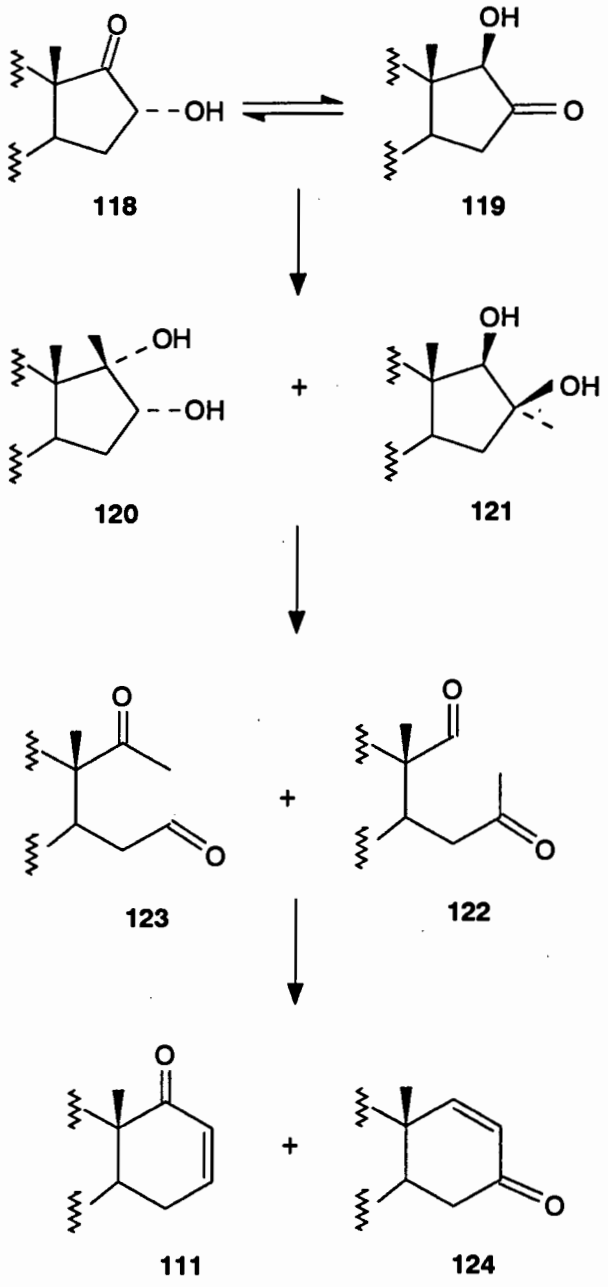
An alternative approach to the more immediate precursor for oxidative cleavage, *viz.* a 17-methyl 16,17-diol, would be feasible via Grignard methylation of a 16-hydroxy 17-ketone. However, it was recognised that regiocontrol during this step was likely to be compromised by the ease with which ring D α-hydroxy ketones undergo isomerisation.[138]

Nevertheless, the 16α-hydroxy 17-ketone (**118**) (prepared by α-bromination of estrone, followed by halide displacement using NaOH-DMF)[131,138] was treated with methylmagnesium iodide to give an inseparable mixture (3:2) of the isomeric methyl diols (**120**) and (**121**) (Scheme 5.25). Spectroscopic data were consistent with the proposed structures, the major product (**120**) constituting the desired 17β-methyl 16α,17α-diol. The stereochemistry at C(16) and C(17) for **120** was assigned on the basis of literature precedent.[139] Recrystallisation of the mixture from ethyl acetate did improve the ratio of **120:121** to 7:1, but it was evident that a substantial amount of regioisomerisation was taking place under the basic conditions required for methylation, indicating that this route would not be practical for the synthesis of 17a-homoestrone (**111**).

A chromatographically clean mixture (3:2) of the methyl diols (**120** + **121**) was treated with either sodium periodate (2 h) or lead(IV) acetate (5 min), both reagents giving a comparable partially separable mixture (2:3, from NMR) of the products of oxidative cleavage. Flash chromatography allowed a small amount of each isomer to be isolated for characterisation purposes. The spectroscopic data identified the 16-methyl-16,17-seco compound (**122**) as the less polar product. The ^{1}H-NMR spectrum showed the 16-Me as a three-proton singlet at δ 2.17, and the aldehydic 17-proton as a singlet at δ 9.37. The isomeric 17-methyl-16,17-seco compound (**123**) had similar NMR characteristics to **122**, with the 17-methyl group resonating at δ 2.19 as a singlet and the aldehydic 16-H appearing at δ 9.81 (br d, *J* 1.7 Hz). This splitting of the aldehyde proton allowed for the distinction between isomers.

The mixture of 16,17-seco-steroids (**122** + **123**) was treated with methanolic potassium hydroxide at 20°C for 30 min to give rise to a partially-separable mixture (1:1 from NMR) of isomeric 17a-homo enones (**111**) and (**124**). The less polar compound was the desired ring D homologated enone (**111**), isolated in 15% overall yield from estrone by this route. The isomeric 17a-homo enone (**124**) was isolated in a similar yield. This compound has been reported several times in the literature.[106,140]

Scheme 5.25



5.4.2 Conversion of the 17a-Homo Enone (111) into the 14,16-Dienone. With an efficient conversion of estrone to the homologated enone (**111**) available, further dehydrogenation of ring D was necessary in order to prepare the 14,16-diene 17a-ketone (**127**) for a study of the regio- and stereoselectivity of conjugate allylation.

The method of choice was considered to be a direct dehydrosilylation of the silyl dienyl ether, derived from the enone (**111**). Palladium catalysed dehydrosilylation of silyl enol ethers derived from simple ketones is a well-known procedure for the synthesis of α,β-

unsaturated ketones, and an extension of this method for the conversion of an enone into the corresponding dienone has recently been reported by Fukumoto.[141]

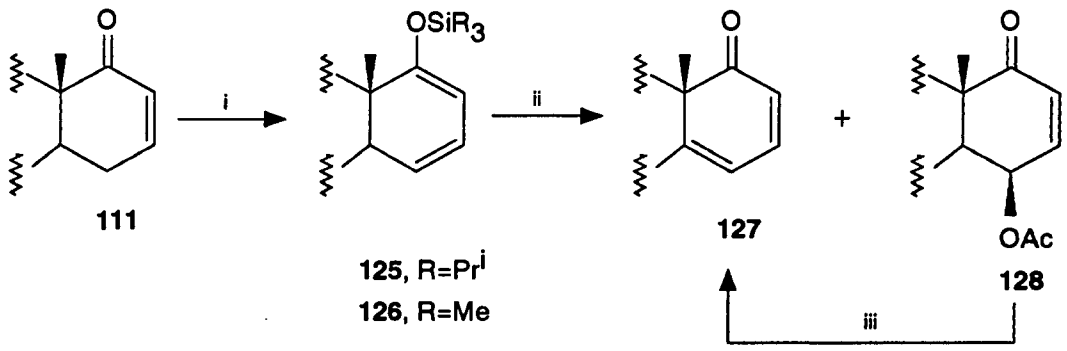
The enone (**111**) was thus exposed to triethylamine and triisopropyl trifluoromethanesulfonate (TIPS-triflate) in dichloromethane at 20°C for 1 h. This produced the TIPS dienyl ether (**125**) in high yield (97%). The enone (**111**) could similarly be converted into the trimethylsilyl dienyl ether (**126**) by treatment with triethylamine and TMS-triflate. A similar result was obtained on low temperature (-78°C) base treatment (LDA) of the enone (**111**), followed by enolate trapping with chlorotrimethylsilane. Both silyl dienyl ethers (**125**) and (**126**) were synthesised since TMS dienyl ethers are known to be unstable; if the TMS derivative (**126**) proved problematical in the dehydrosilylation step, the TIPS compound (**125**) would possess the necessary stability. Key NMR data for **125** and **126** are shown in Table 5.26.

Table 5.26: ^{1}H-NMR Data for Silyl Dienyl Ethers (**125**) and (**126**)

Proton	**125**	**126**
17a-OSiR$_3$	1.11 (3H, s) and 1.14 (18H, d, *J* 1.6 Hz)	0.26 (9H, s)
17-H	5.03 (d, *J* 5.7 Hz)	5.06 (d, *J* 5.6 Hz)
15-H	5.55 (dd, *J* 9.3 and 2.6 Hz)	5.59 (dd, *J* 9.5 and 2.6 Hz)
16-H	5.9 (ddd, *J* 9.3, 5.7 and 2.6 Hz)	5.92 (ddd, *J* 9.5, 5.6 and 3.2 Hz)

Treatment of either the TMS or the TIPS dienyl ether with palladium(II) acetate gave rise to a partially-separable mixture of two products – the 17a-homo dienone (**127**) and an unexpected by-product formulated as the 15β-acetoxy-17a-homo enone (**128**) (Scheme 5.27). The NMR spectrum of **127** confirmed the expected structure, displaying signals for three olefinic protons, 16-H resonating at δ 7.14 (dd, *J* 9.6 and 6.3 Hz) and 15- and 17-H forming an unresolved two-proton multiplet at δ 6.06 (*W* 17.3 Hz). The acetoxy compound (**128**) showed two carbonyl absorption bands in the infrared spectrum at ν_{max} 1677 cm^{-1} (C=O) and 1733 cm^{-1} (OAc). The NMR features of **128** were diagnostic, with 15α-H resonating at δ 5.56 (dd, *J* 5.2 and 2.6 Hz), 17-H at δ 6.06 (d, *J* 10.1 Hz), 16-H at δ 6.87 (dd, *J* 10.1 and 5.2 Hz), and the 15β-OAc group as a singlet at δ 2.07.

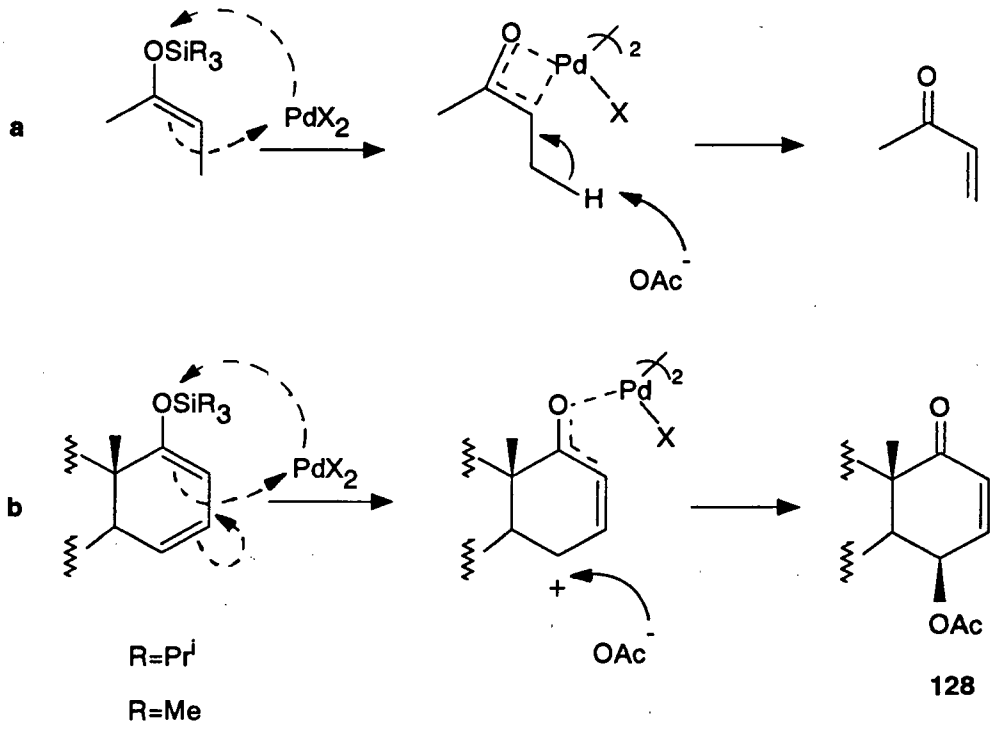
Scheme 5.27



i, SiR_3OTf, NEt_3; ii, $Pd(OAc)_2$; iii, $Pd(OAc)_2$, PPh_3

The mechanism of dehydrosilylation of an enol ether involves an oxo-π-palladium(II) complex (Scheme 5.28, a).[142] This concept can readily be extended to a silyl dienol ether, in which case the 15-carbocationic intermediate can be captured by acetate (Scheme 5.28, b).

Scheme 5.28



It is known that allylic acetates can undergo facile elimination to form dienones by employing a palladium catalyst.[143] Thus, heating of a mixture of the dienone (**127**) and acetoxy enone (**128**) with $Pd(OAc)_2$ and triphenylphosphine in degassed toluene gave rise to a single product, the dienone (**127**) in good yield (80%). Thus, in practice, it was possible to achieve good overall conversion of the enone (**111**) to the dienone (**127**) by subjecting the mixture obtained from the dehydrosilylation step to allylic acetate elimination conditions.

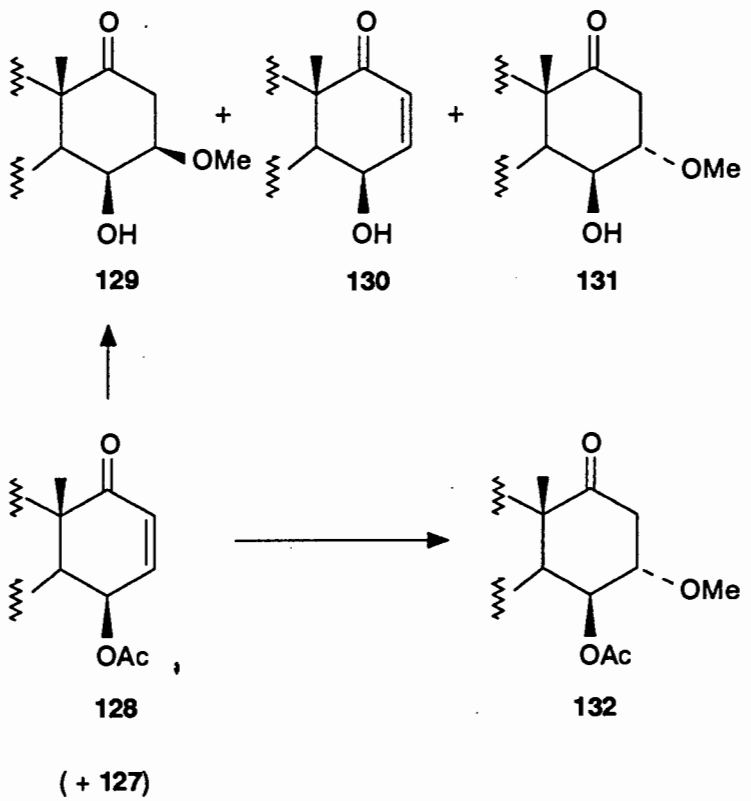
The fact that stoichiometric amounts of palladium were required in the dehydrosilylation step led us to assess the practicality of a catalytic pathway. However, the use of 0.5 equivalents of palladium acetate with *p*-benzoquinone as a co-oxidant[142] was ineffective, the reaction only reaching 50% completion. Attempts to functionalise the enone (**110**) at C(15) (LDA/PhSeCl or NBS) for further elimination led only to multicomponent mixtures. Steroidal ketones have been dehydrogenated to enones using benzeneseleninic anhydride (BSA).[144] Exposure of the enone (**111**) to BSA in refluxing benzene, with or without *m*-iodosobenzoic acid as catalyst, however, only resulted in the recovery of starting material. In an alternative approach, the allylic azidation method of Magnus was attempted, in which a TIPS dienyl ether undergoes β-azidation using TMS-azide and iodosobenzene,[145] followed by elimination of the allylic azide adduct. Applying this reaction to the TIPS dienyl ether (**125**), it was possible to isolate the dienone (**127**) in 15% yield. The fact that the yield was low was unsurprising, since azidation was required to take place at a tertiary centre.

It was evident from the foregoing experiments that the method of choice for formation of the dienone (**127**) involved dehydrosilylation of a silyl dienyl ether, followed by elimination of the allylic acetate.

Experiments were conducted on the dehydrosilylation mixture (**127** + **128**) in order to separate the respective products and to explore the further chemistry of the 15β-acetoxy enone (**128**).

Treatment of a mixture of **127** and **128** with potassium carbonate in methanol at 20°C for 24 h was mistaken, leading to a four-component mixture. On chromatography, the dienone (**127**) eluted first (46%), followed by the 15β-hydroxy-16β-methoxy-17a-ketone (**129**) (4%), the 15β-hydroxy Δ^{16}-17a-ketone (**130**) (13%), and the 15β-hydroxy-16α-methoxy-17a-ketone (**131**) (7%) (Scheme 5.29). Exposure of a mixture of **127** and **128** to methanolic potassium hydroxide, even at low temperatures, only resulted in Michael addition of a methoxy group at C(16) to form the 15β-acetoxy-16α-methoxy-17a-ketone (**132**). These compounds were characterised, but since the reactions were not of interest to the main investigation, this was not pursued further.

Scheme 5.29



5.5 Conjugate Addition Studies

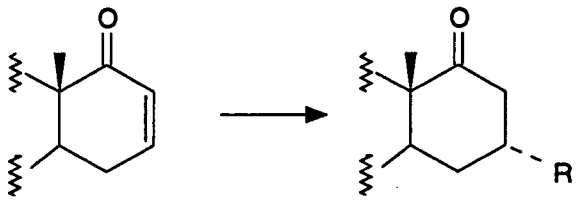
With the dienone (**127**) in hand, we were ready to investigate the 1,6- *vs* 1,4-reactivity of the system, with a view to introducing 14-functionality. Kinetic 1,6-additions have been known to occur in all-*trans* dienones,[146] however no precedent has been found for 1,6-addition to linear cyclohexadienones. We were interested not only in the regiochemical outcome of conjugate addition to the dienone (**127**), but also in the stereoselectivity.

As a preamble to the investigation into conjugate alkylation of the dienone, studies on the enone (**111**) as a model system were undertaken in order to determine reactivity trends.

Conjugate Additions to the Enone (111). Treatment of the enone (**111**) with lithium dimethylcuprate ($LiMe_2Cu$) gave the 16α-methyl-17-ketone (**133**) as a single product in 77% yield (Scheme 5.30). The 16α-methyl group resonated at δ 1.0 (d, *J* 7.1 Hz) in the NMR spectrum of **133**, while the 17-protons were both assigned to

doublets of doublets at δ 2.06 (*J* 14.3 and 4.1 Hz, 17β-H) and 2.8 (*J* 14.3 and 6.2 Hz, 17α-H), the magnitude of the vicinal couplings reflecting a synclinal relationship with 16β-H, and thereby providing evidence for the stereochemical assignment at C(16). This stereochemical configuration at C(16) was consistent with theoretical expectations *viz.* the phenomenon in bicyclic systems in which, because the system is locked into one conformation, steric factors frequently override electronic effects to determine stereoselectivity.[147] Thus, conjugate addition occurs at the face opposite to that bearing the substituent ie. α-face attack opposite the 13β-methyl group and C(14)-C(8) bond in this case.

Scheme 5.30



111

133, R=Me

134, R=CN

135, R=Allyl

Diethylaluminium cyanide (Et_2AlCN) is known to facilitate formation of the thermodynamically-favoured 1,4-hydrocyanation adduct of α,β-unsaturated ketones.[148] Reaction of the enone (**111**) with Et_2AlCN in benzene at 20°C for 2 h was again highly stereoselective, giving rise to the 16α-cyano 17-ketone (**134**) in 62% yield (Scheme 5.30). Spectroscopic data confirmed the regio- and stereochemical outcome of the reaction. The 17α-proton resonated at δ 2.53 (ddd, *J* 14.8, 2.3 and 1.8 Hz), the small coupling (1.8 Hz) arising from a four-bond interaction with 15α-H. The 17β-proton resonated at δ 2.88 (dd, *J* 14.8 and 7 Hz).

Conjugate allylation of an enone using allyltrimethylsilane and a suitable Lewis acid to cleave the Si-C bond of the allylsilane is the basis of the Sakurai reaction. In general, titanium(IV) chloride ($TiCl_4$) is the preferred catalyst for addition to cycloalkenones; tetrabutylammonium fluoride (TBAF) has been shown to be less regioselective than $TiCl_4$.[149]

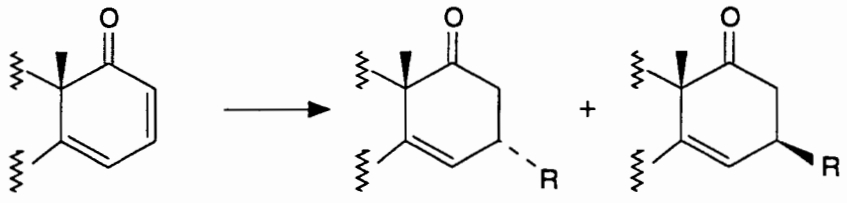
Reaction of the enone (**111**) with allyltrimethylsilane and $TiCl_4$ at -78°C for 4 h was incomplete, giving rise to stereoselective 1,4-allylation from the α-face in 42% yield (Scheme 5.30). The success of the reaction was confirmed by the allyl group signals in

the NMR spectrum at δ 5.0 (2H, m, 3'-H_2) and 5.73 (dddt, *J* 18.5, 11.2 and 2 x 7 Hz, 2'-H). A similar reaction outcome was obtained when the enone was treated with TBAF prior to the addition of allyltrimethylsilane and HMPA. After 30 min at 20°C, the allyl ketone (**135**) had formed in 48% yield.

The foregoing results emphasise that conjugate addition to the enone (**110**) is highly regio- and stereoselective. Similar reactions were performed on the dienone (**127**) in order to determine the preferred mode of conjugate alkylation of this system.

Conjugate Additions to the Dienone (127). The copper-catalysed Grignard reagent is known for its high reactivity. Great improvements in the reactivity of organocopper reagents have been noted when additives such as dimethyl sulfide (improves solubility and stabilises the organocopper) and chlorotrimethylsilane (along with a polar solvent eg. HMPA or TMEDA) are combined with the copper-catalysed Grignard reagent.[150] Reaction of the dienone (**127**) with MeMgI/CuI.DMS/TMSCl/HMPA at 0°C for 30 min yielded an inseparable mixture (1:1, from NMR) of 1,4-addition products in 69% yield (Scheme 5.31). Two recrystallisations concentrated one isomer (**136**) with respect to the other (**137**). The NMR data for these epimers is summarised in Table 5.32.

Scheme 5.31



127

136, **137**, R=Me

138, **139**, R=CN

141, **142**, R=Allyl

143, **144**, R=Acetonyl

From models, a 16α-methyl group would give rise to a large ($J_{16\beta\text{-}17\alpha}$ = *ca* 9 Hz) and a smaller ($J_{16\beta\text{-}17\beta}$ = *ca* 5 Hz) coupling, whereas a 16β-methyl substituent would create two medium-sized (*ca* 6 Hz) couplings between 16α-H and the 17-protons. This allowed a tentative assignment of the stereochemistry at C(16), even though the dichotomy in coupling sizes was not as pronounced as that suggested by models.

Table 5.32: Key NMR Data for Methyl Enones (**136**) and (**137**)

Proton	**136** (16α-Me)	**137** (16β-Me)
16-Me	δ 1.1 (d, *J* 6.9 Hz)	δ 1.05 (d, *J* 7.1 Hz)
17β-H	δ 2.38 (dd, *J* 12.8 and 9.3 Hz)	δ 2.25 (dd, *J* 14.9 and 8.7 Hz)
17α-H	δ 2.5 (dd, *J* 12.8 and 5.5 Hz)	δ 2.67 (dd, *J* 14.9 and 6.1 Hz)
15-H	δ 5.44 (br d, *J* 2.8 Hz)	δ 5.48 (d, *J* 2.1 Hz)

A similar reaction outcome was obtained by 1,4-methylation with lithium dimethylcuprate ($LiMe_2Cu$) ie. a 1:1 mixture of Δ^{14}-16-methyl-17a-ketone epimers (**136** + **137**) was formed. This lack of stereoselectivity was not unexpected in view of the flattened nature of the 17a-homo dienone which minimises the steric factors which would usually determine the face selectivity.

Reaction of the dienone (**127**) with Et_2AlCN in benzene at 20°C for 2 h, gave rise to two partially separable products, identified as the 1,4-hydrocyano adducts (**138**) and (**139**) from spectroscopic data (Scheme 5.31). Table 5.33 summarises the NMR data for the cyano-adducts.

Table 5.33: Key NMR Data for Cyano Enones (**138**) and (**139**)

Proton	**138** (16α-CN)	**139** (16β-CN)
16-H	δ 3.68 (*W* 20 Hz)	δ 3.71 (*W* 20 Hz)
17β-H	δ 2.78 (dd, *J* 13.7 and 6 Hz)	δ 2.81 (dd, *J* 13.8 and 7.7 Hz)
17α-H	δ 2.94 (dd, *J* 13.7 and 8.4 Hz)	δ 2.87 (dd, *J* 13.8 and 6.1 Hz)
15-H	δ 5.57 (d, *J* 3.7 Hz)	δ 5.57 (dd, *J* 3.6 and 1.5 Hz)

The stereochemistry at C(16) of the cyano enones (**138**) and (**139**) was assigned by comparison of the 15-H signals of both epimers. 15-H resonated as a doublet (*J* 3.7 Hz) in the spectrum of **138** and as a dd (*J* 3.6 and 1.5 Hz) in that of **139**. An equatorial 16-cyano group (ie. 16α-CN) creates an orthogonal relationship between 16β-H and

15-H. The 15-proton would thus only show the allylic coupling to 8β-H (3.7 Hz) in this case. The epimer (**139**) has a vicinal dihedral angle consistent with $J_{15,16\beta}$=1.5 Hz. The allylic $J_{15,8\beta}$ coupling (*J* 3.6 Hz) was comparable to that found for **138**.

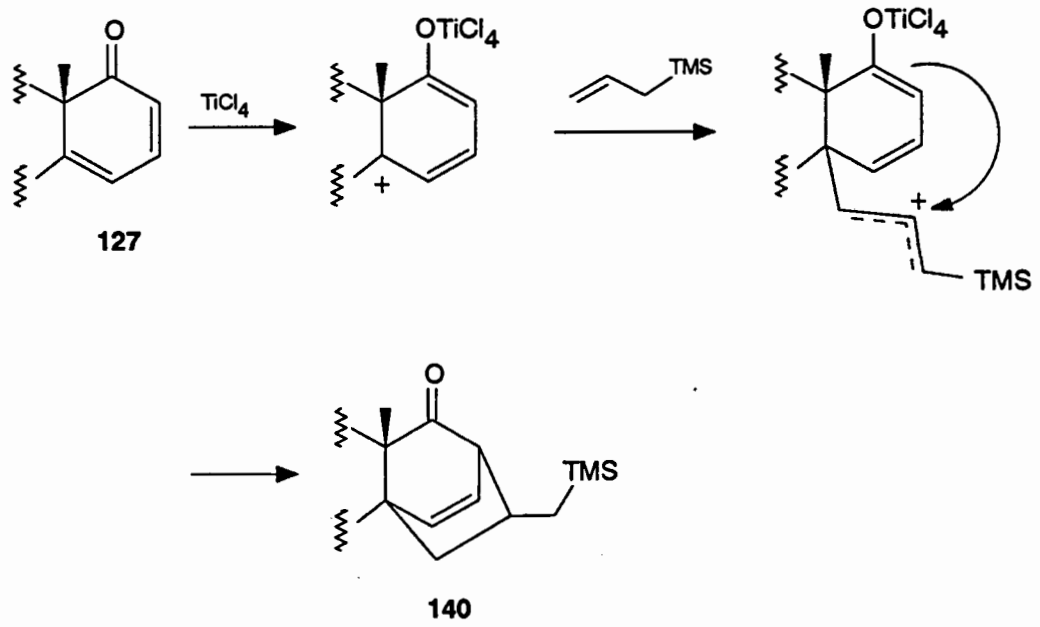
Reaction of the dienone (**127**) with allyltrimethylsilane and $TiCl_4$ at -78°C gave a partially-separable two-component mixture in 88% overall yield. The more polar material comprised a mixture (1:1 from NMR) of the 1,4-allylation epimers (**141** and **142**) (*ca* 70%) (Scheme 3.31).The inseparable 1,4-adducts (**141** + **142**) exhibited coincidental allyl signals at δ 5.0-5.15 (2H, m, 3'-H_2) and δ 5.77 (1H, m, 2'-H), and the epimeric 15-protons resonated at δ 5.48 and 5.51 (each d, *J* 2.4 Hz). The less polar compound (**140**) (*ca* 18%) was formulated as the product of a [3 + 2] annulation (Scheme 5.34). Spectroscopic evidence supported this structure. The infrared spectrum of **140** showed a carbonyl absorption band at ν_{max} 1702 cm^{-1} (cyclohexanone carbonyl group), and the molecular ion (m/z 408) indicated a molecular formula of $C_{26}H_{36}O_2Si$. The 1'-TMS group resonated as a nine-proton singlet at δ 0.02, and the 1'-protons as a multiplet at δ 0.56 in the ^{1}H-NMR spectrum. 16-H resonated at δ 6.06 (dd, *J* 8 and 6.6 Hz) , and 15-H at δ 6.46 (d, *J* 8 Hz) . COSY and HETCOR data located the 17^2-protons at δ 1.12 (dd, *J* 12.5 and 6.4 Hz) and 1.85 (dd, *J* 12.5 and 8.9 Hz), and 17^1-H resonated as a multiplet at δ 2.18.

Literature precedent provided further substantiation of the structure proposed for compound **140**. Danheiser[151] has established methodology for similar [3 + 2] annulations employing conjugated enones and trialkylallylsilanes. The basis of this process involves electrophilic addition to the organosilane, followed by cyclisation with a secondary carbocation (Scheme 5.34).

The noteworthy aspect of this side reaction is that an initial 1,6-addition must have occurred, implying that the 17a-homo compound (**127**) *can* allow 1,6-addition to the s-*cis* dienone. The $TiCl_4$ catalyst facilitates this reaction by competing for the lone pairs on oxygen instead of desilylating the allyltrimethylsilane. This was confirmed by treating the dienone (**127**) with TBAF and allyltrimethylsilane. Only the 1,4-allylation products (**141**) and (**142**) were formed, again in a 1:1 ratio of epimers.

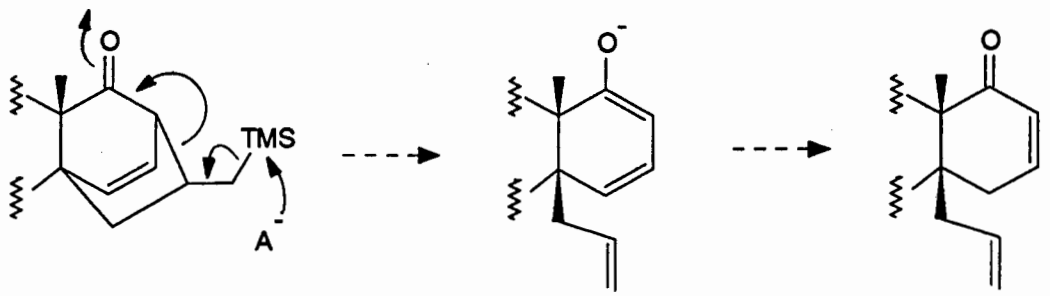
We reasoned that, if the C-Si bond of compound **140** could be cleaved, then the resultant carbanion would rearrange, giving rise to the target 14-allyl 17a-homo enone (Scheme 5.35).

Scheme 5.34



127 **140**

Scheme 5.35



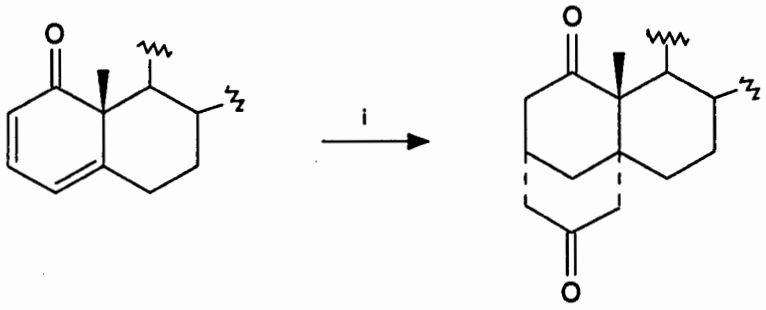
140

Treatment of the annulation product (**140**) with TBAF over molecular sieves in either tetrahydrofuran or DMF/HMPA as solvents, using temperatures of up to 80°C,[152] resulted only in the recovery of starting material. A 'pull-push' concept, employing cerium(III) chloride to enhance the electrophilicity of C(17a), and a fluoride ion source to cleave the C-Si bond, was equally ineffectual. No further attempts were made owing to a lack of material. If the formation of compound **140** or an analogous compound could be optimised, it may be rewarding to investigate other means of cleaving the relevant bond thereby facilitating access to the 14-allyl target molecule.

A report by Hanson[153] on the addition of acetone across a linear steroidal ring A dienone prompted us to attempt the analogous reaction on the dienone (**127**), since

Hanson's result implied 1,6-addition, followed by Michael closure with the residual conjugated enone (Scheme 5.36).

Scheme 5.36



i, acetone, HCl, Δ

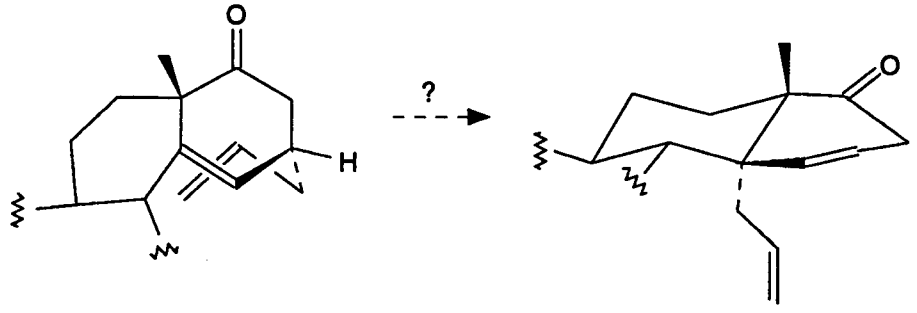
Treatment of the dienone (**127**) with refluxing acetone containing a catalytic amount of concentrated hydrochloric acid for 5 h gave an inseparable mixture (1:1 from NMR) of 1,4-acetonyl adducts (**143** + **144**) in 57% yield (Scheme 5.31). The remainder of the material comprised starting material, since prolonged reaction times resulted in decomposition. The ^{1}H-NMR spectrum of the mixture confirmed the structure, indicating the 15-H of each epimer as a broad singlet at δ 5.49 and 5.50, and the acetonyl methyl groups at δ 2.14 and 2.16 (each 3H, s). The outcome of this reaction implies protonation of acetone, giving rise to an enol species, along with protonation of the 17a-ketone which would enhance the electrophilicity of C(16). Similar treatment of the enone (**111**), however, even on prolonged reflux, gave no indication of any product formation. The Hanson findings thus appear to be at variance with our results.

In conclusion, these results have demonstrated that the enone (**110**) undergoes exclusive 1,4-addition from the α-face of ring D. The dienone (**127**), on the other hand, was consistently unstereoselective towards conjugate addition probably owing to the flattening of the six-membered D-ring. The regioselectivity of addition to the dienone was generally 1,4-, although a 1,6-addition was implicated in the formation of compound **140**.

5.5.1 Attempts to Transpose the 16-Allyl Group to C(14) by Sigmatropic Rearrangement. Literature precedent for the transposition of an allyl group around a six-membered ring[154] suggested that a similar [3,3] sigmatropic rearrangement of the 16-allyl Δ^{14}-17a-ketone would transfer the allyl group to C(14). From models, a 16α-allyl group possesses a favourable stereochemical disposition to C(14), creating a chair-like

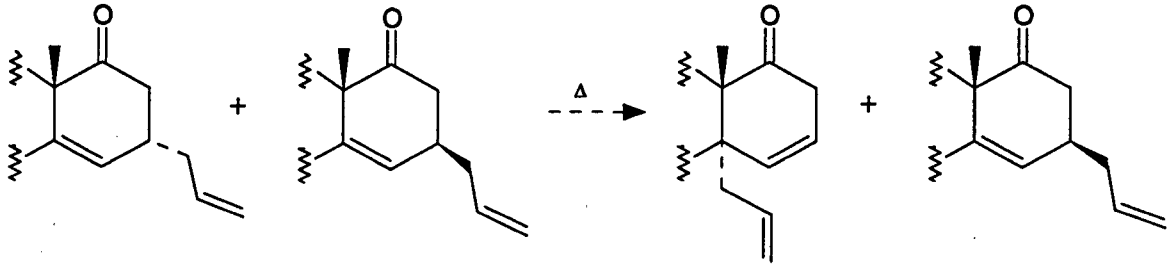
transition state with the 1,5-removed double bonds, whereas a similar rearrangement of the 16β-allyl isomer did not seem feasible in terms of alignment if the 1,5-diene system (Scheme 5.37).

Scheme 5.37



The lack of α-stereoselectivity in the conjugate allylation of the dienone (**127**) was thus disappointing. It did seem viable, however, to selectively effect a Cope rearrangement of the 16α-allyl component of the mixture of epimers (**141** + **142**), and then separate the 14α-allyl enone from the unreacted 16β-allyl compound (Scheme 5.38).

Scheme 5.38

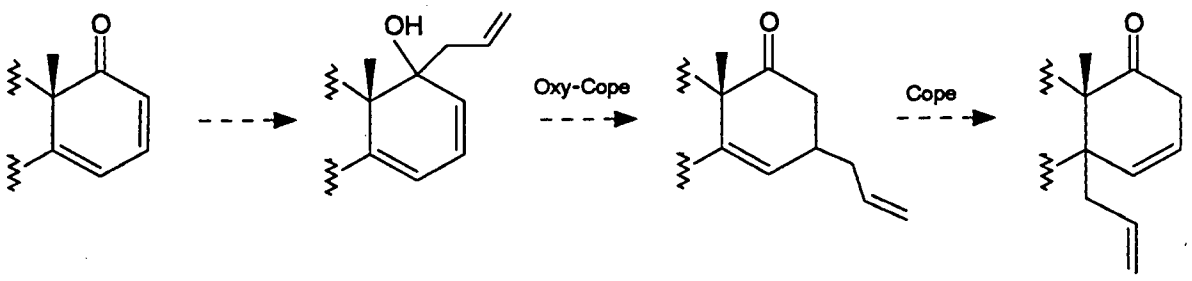


The Cope rearrangement is thermally-mediated.[155] However, heating of the allyl enone mixture (**141** + **142**) in degassed toluene in a sealed tube at 260°C for 16 h was fruitless, NMR examination of the recovered material indicating the lack of reaction. If the mixture was heated to 400°C in decalin for 24 h, however, only decomposition was observed. This route was abandoned owing to a lack of material, but it would be interesting to examine a broader range of solvent/temperature/time reaction conditions.

A recent report by Paquette and Geuvel[156] on tandem Cope-Cope rearrangements prompted an attempt to introduce an allyl group at C(14) of the dienone by 1,2-allylation

at C(17a) followed by either tandem or sequential oxy-Cope-Cope rearrangements (Scheme 5.39).

Scheme 5.39



Treatment of the dienone (**127**) with allylmagnesium chloride at 20°C for 1 h gave rise to a major product (TLC). Any attempt to purify this product, however, resulted in decomposition to extremely polar material, comprising inseparable mixtures. One of the possible products of this mixture could be the conjugated tetraene formed by dehydration of the 17a-alcohol formed on 1,2-allylation. No products were, however, identified owing to large amounts of inseparable impurities.

If the Grignard product was isolated by work-up and subjected to oxy-Cope conditions (KH, I_2, 18-crown-6 in refluxing dioxane) without further attempts at purification, only a multicomponent mixture was obtained. This route was thus also abandoned.

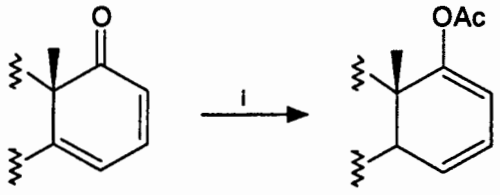
5.6 Preliminary Cycloaddition Studies on 17a-Homo Dienes

Ring D dienes, as mentioned in chapter 2, are known to be reactive towards dienophiles. It was thus of interest to ascertain if this reactivity was extended to the 17a-homo diene system. Substrates for these exploratory cycloaddition studies included the TIPS- and TMS-dienyl ethers (**125**) and (**126**), the dienone (**127**), and the dienyl acetate derivative (**145**) (Scheme 5.40).

The 15,17-dienyl 17a-acetate (**145**) was expected to be more stable than the silyl dienyl ethers, but was synthesised in low yield (11%) by subjecting the enone (**111**) to forcing enol acetylation conditions (*viz.* acetic anhydride, isopropenyl acetate, catalytic *p*-TsOH, reflux) for 5 h. Prolonged reaction peroids resulted is decomposition. The ^{1}H-NMR data of the dienyl acetate was similar to those of the trialkylsilyl dienol ethers (**125** and **126**). Attempts to trap the dienolate anion of the enone (formed by reaction of the

enone with LDA) with acetyl chloride was ineffective as an alternative route to the dienyl acetate (**145**).

Scheme 5.40

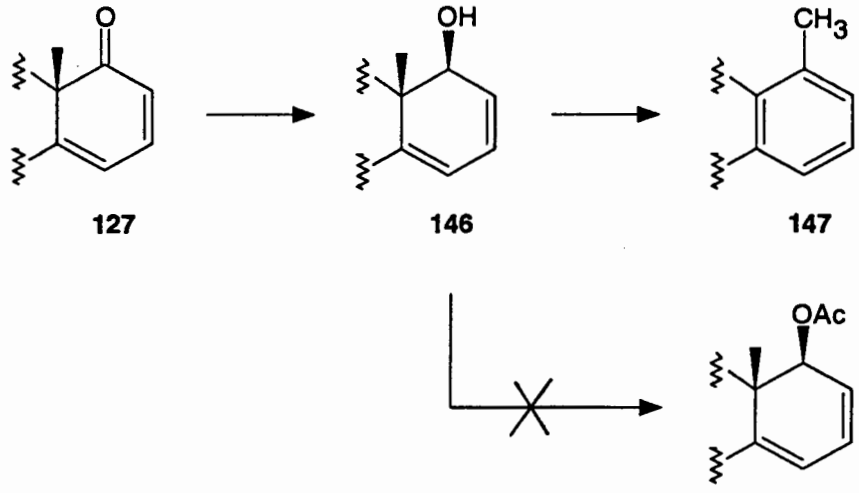


127 **145**

i, Ac_2O, IPA, TsOH, Δ

In order to improve the reactivity of the dienone (**127**) towards cycloaddition, an attempt was also made to synthesise the dienyl acetate derivative of the dienone, *viz.* the $\Delta^{14,16}$-dienyl-17a-acetate (Scheme 5.41).

Scheme 5.41

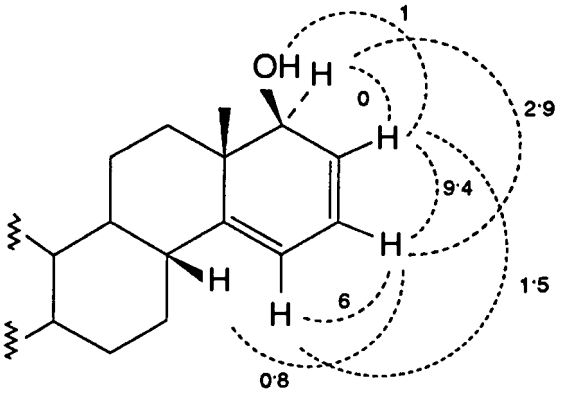


127 **146** **147**

Cerium-mediated 1,2-reduction of the dienone (**127**) with sodium borohydride at 0°C for 1 h produced the 17aβ-alcohol (**146**) in moderate yield (70%). The stereochemistry at C(17a) was assigned on the basis of the NMR spectrum of **146**. The 17a-proton resonated at δ 4.37 as a broad singlet. From models, a 17aβ-OH gives rise to an orthogonal $H_{17a\alpha}$-H_{17} interaction. A 17aβ-proton would show substantial vicinal coupling to 17-H, though. The 17-proton resonated at δ 5.64 (ddd, *J* 9.4, 1.5 and 1 Hz),

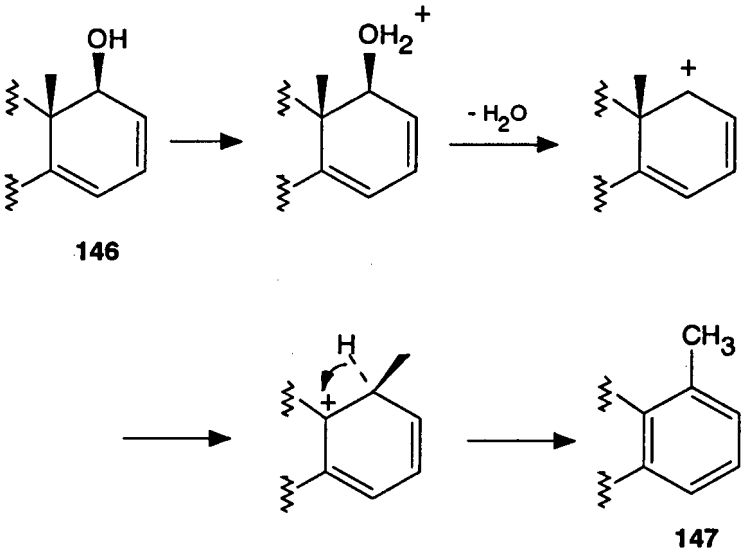
simplifying on D_2O exchange to a dd, thereby losing the smallest coupling (1 Hz) to the 17a-OH. The signal at δ 5.76 (dd, *J* 6 and 1.5 Hz) was assigned to 15-H, and that at δ 5.88 (dddd, *J* 9.4, 6, 2.9 and 0.8 Hz) to 16-H (Figure 5.42).

Figure 5.42



This 17aβ-alcohol (**146**) was unstable, thereby preventing full characterisation. Direct treatment of the dienyl alcohol (**146**) (isolated by work-up) with acetic anhydride in pyridine, gave rise to a multicomponent mixture. The only product isolated from this mixture was an aromatised ring D compound (**147**), probably formed through the intermediacy of a 17a-carbocationic species (Scheme 5.43).

Scheme 5.43



The ^{1}H-NMR spectrum of **147** indicated the absence of the 13β-methyl singlet, but the presence of a lower-field methyl singlet at δ 2.29. The aromatic region of the spectrum displayed the usual ring A aromatic proton signals, along with an unresolved three-proton multiplet at δ 7.03-7.25 for the ring D aromatic protons. All other data was consistent with the proposed structure for **147**.

This unsatisfactory result, as well as time constraints, prompted us to commence the cycloaddition studies using the substrates available. Preliminary experiments designed to test the reactivity of the trialkylsilyl dienyl ethers (**125**) and (**126**), the dienyl acetate (**145**), and the dienone (**127**) towards cycloaddition with various dienophiles (phenyl vinyl sulfone, acrolein with $BF_3.Et_2O$ catalysis, and nitroethylene) failed. Typically, the dienyl acetate (**145**) and dienone (**127**) were recovered unchanged after each attempted reaction, whereas the silyl dienyl ethers (**125**) and (**126**) reverted substantially to the enone (**111**). The reactivity of the ring D dienes thus appears to be suppressed, and the lack of rectivity is exacerbated by the lability of the silyl dienyl ethers.

5.7 Conclusions

Despite the failure to reach the target 14-allyl 17a-homo derivative of estrone, this chapter has documented several new aspects of the ring D reactivity of the systems investigated. Attempts to expand ring D of the allyl enone (**17**) or the allyl ketone (**18**) were frustrated by inappropriate regioselectivity. However, further work is warranted in order to investigate more controlled methods of ring expansion of these substrates. In the second approach, ring expansion of estrone 3-methyl ether was described, leading to a successful synthesis of 3-methoxy-17a-homoestra-1,3,5(10),16-tetraen-17a-one (**111**), which was converted into the $\Delta^{14,16}$-dienyl 17a-ketone derivative (**127**) as a substrate for exploratory studies into the conjugate reactivity of this system.

Chapter 6

BINDING AFFINITY STUDIES

This work has led to the synthesis of novel 14β,17β-propano and cyclopenta[14,15] estradiols, along with functional variants thereof. The estradiol and 'estriol' analogues were submitted for receptor-binding assays. The receptor, in this case the estrone receptor, is used as a yardstick to gauge, compare and classify biological reponses. The binding affinity assays are thus an integral part of any structure-activity study.

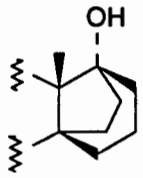
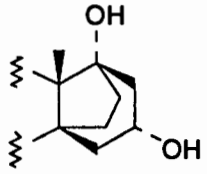
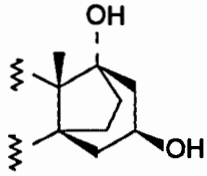
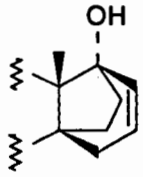
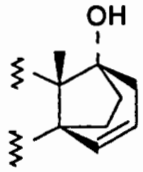
The affinities of the estradiol and 'estriol' analogues were determined by the method of competitive protein binding.[158] This technique requires radioactively labelled reference hormone. The proportion of reference material bound by the receptor protein decreases on addition of the test substance, as the test compound competes for receptor site occupancy. This competition depends on the concentration of the test material and upon its affinity towards the receptor. The affinity is measured in terms of a 'competition factor' (CF), which is defined as the ratio of the concentration of the test sample (c_{test}) and that of the reference substance (c_{ref}) required for 50% competition:

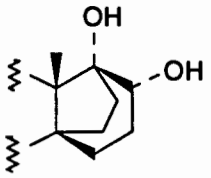
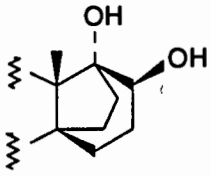
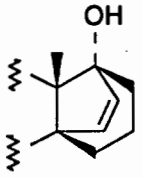
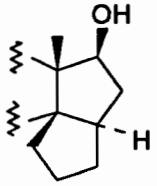
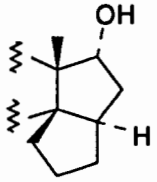
$CF=(c_{test}/c_{ref})$ at 50% competition

Estradiol was taken as the reference hormone, and thus has a CF=1. A binding assay result of $CF \leq 1$ indicates that the hormone analogue competes successfully against estradiol at the receptor site, whereas a compound with CF much higher than unity would not normally be considered a potentially biologically active analogue.

Table 6.1 summarises the binding affinity results for the hormone analogues synthesised in this work.

Table 6.1: Competition Factors for Estradiol Analogues

Compound	Competition Factor
 **24**	69
 **27**	∞
 **28**	∞
 **32**	318
 **33**	470

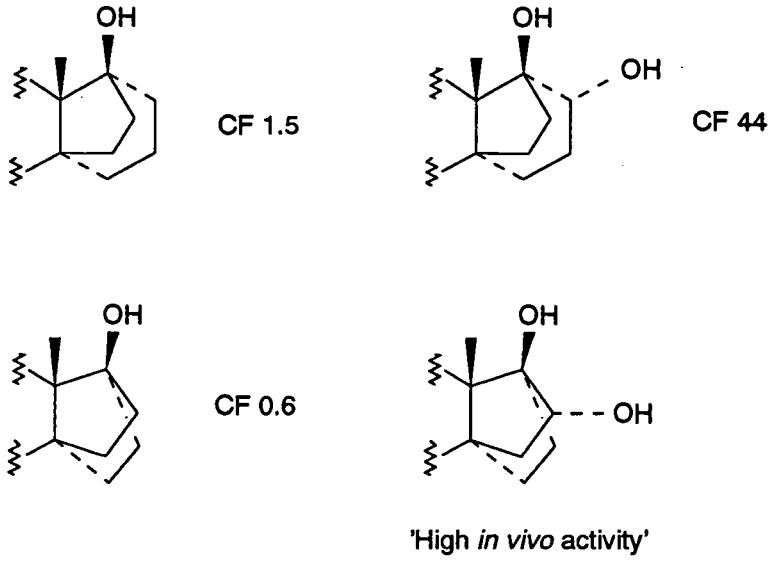
Compound	Competition Factor
 **53**	360
 **54**	>500
 **67**	65
 **77**	1.3
 **78**	7.4

Note: All structures have 3-OH

It is clear from these results that, in terms of structure activity relationships, the 14β,17β-propano bridge is a negative feature, and that functional variations on either bridge only serve to decrease binding affinity further. These data are important for the definition of boundary conditions in ring D bridged analogues. It is of interest to compare some of the CF values measured for the 14α,17α-ethano and propano bridged estradiols and estriols (Figure 6.2).[14,16] Homologation of the β-face bridge may interfere sterically

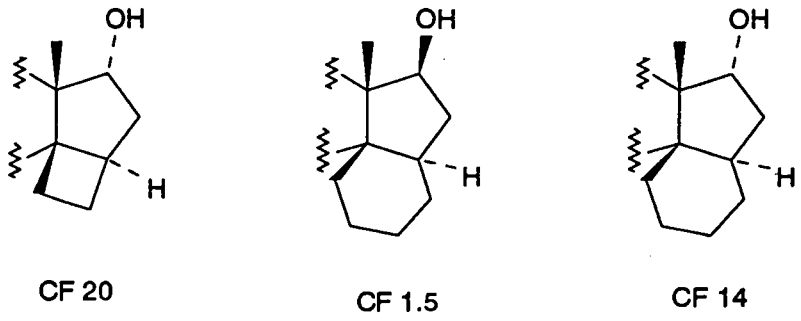
with binding at the estrone receptor site, or may displace the 17-OH group out of the favoured alignment.

Figure 6.2



The cyclopenta[14,15] 3,17β-estradiol (**77**), however, showed promising affinity for the receptor site. This is consistent with other 14β,15β-fused ring estradiols (Figure 6.3).[70,72] Unfortunately, the cyclobuta[14,15] 3,17β-estradiol analogue was prepared as a very minor product of the reduction of the precursor 17-ketone, and the small quantity precluded biological evaluation.

Figure 6.3



Chapter 7

EXPERIMENTAL

Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70 eV with an accelerating voltage of 4 kV and a source temperature of either 100 or 200°C. All ^{1}H-NMR spectra were recorded in deuteriochloroform, unless otherwise specified, with tetramethylsilane as internal standard on a Varian VXR-200 instrument at 200 MHz or a Varian Unity spectrometer at 400 MHz, while all ^{13}C-NMR spectra were recorded on the same instruments at 50 or 100 MHz. Melting points were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Microanalysis for C, H and N was performed using a Heraues CHN-rapid combustion analyser. Thin layer chromatography was performed on aluminium-backed silica gel 60 F_{254} plates in various solvent systems using the ascending technique. Upon development, the plates were sprayed with ceric ammonium sulphate in 8M sulphuric acid and baked at 200°C. Column chromatography was carried out using Merck Kieselgel 60: 70-230 mesh for gravity columns, and 230-400 mesh for flash chromatography. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter using chloroform solutions unless otherwise specified. Infrared spectra were recorded in chloroform on a Perkin-Elmer 983 Infrared spectrometer over the range 4000-600 cm^{-1}; solution cells were used in all cases.

The standard 'work-up' implies multiple (three to five times) extraction into the specified solvent, followed by successive washing of the combined organic phase with saturated aqueous sodium hydrogen carbonate and brine, followed by drying of the organic layer by passing the solution through a cone of anhydrous magnesium sulfate in fluted filter paper. The solvent is then removed under reduced pressure.

The following abbreviations have been used: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; tt, triplet of triplets.

Molecular modelling computational results were obtained using software programmes from Biosym Technologies of San Diego – dynamics calculations were done with the *Discover*® programme using the CFF91 force field, *ab initio* calculations were done with the *DMol* programme, and graphical displays were obtained from the *Insight*® *II* molecular modelling system.

Cycloaddition of the Dienyl Acetate (**1**) *with Acrolein*

a) Boron trifluoride-diethyl ether complex (0.02 cm^3, 0.2 mmol) in dry toluene (1 cm^3) was added to the dienyl acetate (**1**) (1 g, 3.1 mmol) and acrolein (0.52 cm^3, 7.7 mmol) in toluene (13 cm^3) at 0°C under nitrogen. The reaction mixture was stirred for 22 h at 20°C, then ice-water was added, and the products were extracted into ethyl acetate. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure, to yield a colourless, crystalline residue (1.06 g). The material was crystallised from acetone-hexane to yield 17β-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbaldehyde* (**2**) (744 mg, 64%), m.p. 173-175°C (lit.[27] 183-185°C)*; $[\alpha]_D$ +100° (*c* 1.0); ν_{max} 1730 (OAc) and 1710 (16^1-CO) cm^{-1}; δ_H (200 MHz) 1.0 (3H, s, 13β-Me), 2.13 (3H, s, 17β-OAc), 2.48 (1H, td, *J* 2 x 11.1 and 4.1 Hz, 9α-H), 2.82-2.93 (2H, m, 6-H_2), 3.09 (1H, dt, *J* 8.7 and 2 x 4.4 Hz, 16β-H), 3.78 (3H, s, 3-OMe), 6.22 and 6.37 (each 1H, d, *J* 6.3 Hz, 17^1- and 17^2-H), 6.64 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H), 7.21 (1H, d, *J* 8.7 Hz, 1-H) and 9.49 (1H, d, *J* 4.4 Hz, 16^1-H) (Found: C, 75.5; H, 7.5%; M^+, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; M, 380).

Chromatography of the mother-liquor residue (400 mg) on silica gel (40 g) with ethyl acetate-toluene (1:19) as eluent yielded 17β-*acetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16β-*carbaldehyde* (**3**) (27 mg, 2%), m.p. 108-112°C (from dichloromethane-toluene); $[\alpha]_D$ +124° (*c* 0.8); ν_{max} 1732 (OAc) and 1710 (16^1-CO) cm^{-1}; δ_H (200 MHz) 0.82 (3H, s, 13β-Me), 2.19 (3H, s, 17β-OAc), 2.48 (1H, td, *J* 2 x 10.5 and 4.2 Hz, 9α-H), 2.83-2.92 (2H, m, 6-H_2), 3.11 (1H, dd, *J* 9.4 and 4.5 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 6.12 and 6.4 (each 1H, d, *J* 6 Hz, 17^1- and 17^2-H), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.4 Hz, 2-H), 7.2 (1H, d, *J* 8.4 Hz, 1-H) and 9.89 (1H, s, 16^1-H) (Found : M^+, 380.200. $C_{24}H_{28}O_4$ requires M, 380.199). This was followed by mixed fractions (220 mg) and further 16α-carbaldehyde (**2**) (50 mg).

b) The reaction was carried out on the dienyl acetate (**1**) (7 g, 21.6 mmol), and worked up as described in the foregoing experiment. The solid residue (8.43 g) was crystallised from dichloromethane-methanol to give the 16α-carbaldehyde (**2**) (5.01 g, 61%). The mother liquor residue (4.43 g) was chromatographed on silica gel (237 g) using ethyl acetate-

* Despite repeated recrystallisations in a variety of solvents, the discrepancy in m.p. remained

toluene (1:19) as eluent to yield unreacted dienyl acetate (**1**) (192 mg, 3%), 16β-carbaldehyde (**3**) (130 mg, 2%), 16α-carbaldehyde (**2**) (685 mg, 8%), and 3-*methoxy*-16α-(16^1,16^1-*dimethoxymethyl*)-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**4**) (1.97 g, 21%), m.p. 118-119°C (dichloromethane-methanol); $[\alpha]_D$ +108° (*c* 1.3); ν_{max} 1734 (OAc) cm^{-1}; δ_H (300 MHz) 0.95 (3H, s, 13β-Me), 2.09 (3H, s, 17β-OAc), 2.48 (1H, td, *J* 2 x 12.3 and 3.8 Hz, 9α-H), 2.76 obsc (1H, dt, *J* 2 x 8.6 and 3.9 Hz, 16β-H), 2.83-2.9 (2H, m, 6-H$_2$), 3.28 and 3.31 [each 3H, s, 16^1-(OMe)$_2$], 3.77 (3H, s, 3-OMe), 4.13 (1H, d, *J* 8.6 Hz, 16^1-H), 6.02 and 6.42 (each 1H, d, *J* 6.4 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.66 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.2 (1H, d, *J* 8.6 Hz, 1-H); δ_C (75 MHz) 170.0 (s, 17-O*C*OMe), 157.5 (s, C-3), 137.8 (s, C-5), 132.5 (s, C-10), 131.6 and 131.4 (each d, C-17^1 and C-17^2), 127.0 (d, C-1), 113.8 (d, C-4), 111.7 (d, C-2), 106.2 (d, C-16^1), 95.0 (s, C-17), 61.3 (s, C-13), 55.2 (q, 3-OMe), 54.3 (s, C-14), 53.1 and 51.9 (each q, 16^1-OMe$_2$), 44.5 (d, C-16), 39.9 (d, C-8), 39.3 (d, C-9), 31.2 (t, C-12), 30.2 (t, C-6), 29.3 (t, C-15), 27.1 (t, C-11), 23.7 (t, C-7) and 14.6 (q, 3-OMe) (Found: C, 73.2; H, 7.8%; M$^+$, 426. $C_{26}H_{34}O_5$ requires C, 73.2; H, 8.0%; M, 426).

Deprotection of the Dimethyl Acetal (**4**)

Isobutylene gas was bubbled through chloroform (0.5 cm^3) under nitrogen. Trimethylsilyl iodide (*ca* 0.032 cm^3) was added, and the solution was stirred for 10 min. Dimethyl ketal (**4**) (100 mg, 0.23 mmol) was added as a solution in isobutylene-saturated chloroform, and the reaction was stirred for 30 min. Saturated aqueous sodium hydrogen carbonate was added, and the yellow colour, due to free iodine, was discharged with saturated sodium thiosulfate. The mixture was extracted with chloroform, and the organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to yield the cycloadduct (**2**) (87 mg, 100 %), m.p. 170-173°C (from chloroform-methanol).

17β-*Acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16α-*carbaldehyde* (**5**)

The 16α-carbaldehyde (**2**) (836 mg, 2.2 mmol) in ethyl acetate (90 cm^3) at 25°C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%, 238 mg). After 90 min the reaction was complete (TLC), and the mixture was filtered. The filtrate was evaporated under reduced pressure to yield the 14α,17α-*ethano compound* (**5**) (818 mg, 97%), m.p. 151-154°C (from acetone-hexane); $[\alpha]_D$ +7° (*c* 1.0); ν_{max} 1728 (OAc) and 1712 (CO) cm^{-1}; δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 2.08 (3H, s, 17β-OAc), 2.82-2.89 (2H, m, 6-H$_2$), 3.02 (1H, br dq, *J* 11.5 and 3 x 3.5 Hz, 16β-H), 3.77 (3H, s,

3-OMe), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.7 Hz, 2-H), 7.21 (1H, d, *J* 8.8 Hz, 1-H) and 9.92 (1H, d, *J* 3.6 Hz, 16^1-H) (Found: C, 74.9; H, 7.5%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.8; H, 7.4%; M, 382).

b) The total cycloaddition fraction from chromatography (660 mg, 1.74 mmol) was subjected to hydrogenation in a similar manner to that described above. Chromatography of the residue isolated after work-up (664 mg) on silica gel (33 mg) using ethyl acetate-toluene (1:19) yielded the dihydro compound (**5**) (460 mg) (70%). This was followed by mixed fractions (130 mg) and then by a minor component which was tentatively assigned the structure 17β-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-16β-carbaldehyde (**6**) (39 mg, 6%), δ_H (200 MHz) 0.72 (3H, s, 13β-Me), 2.13 (3H, s, 17β-OAc), 2.58-2.68 (1H, br td, 9α-H), 2.82-2.91 (2H, m, 6-H_2), 3.21 (1H, dd, *J* 9.3 and 6.5 Hz, 16α-H), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H) and 9.8 (1H, s, 16^1-H) (Found: M^+, 382. $C_{24}H_{30}O_4$ requires M, 382).

Hydride Reductions of the Cycloadduct (**2**)

a) Lithium aluminium hydride (520 mg, 13.7 mmol) was added in small portions to a stirred solution of the 16α-carbaldehyde (**2**) (1.04 g, 2.7 mmol) in dry tetrahydrofuran (65 cm^3) at 0°C under nitrogen. The mixture was stirred at 20°C for 20 min after which the reaction mixture was cooled to 0°C. Saturated sodium sulfate was added dropwise until a white precipitate was obtained. Diethyl ether (10 cm^3) was added, and the mixture was allowed to stir for 30 min. The mixture was filtered under pressure through layers of anhydrous magnesium sulfate and Celite. The filter pad was washed repeatedly with hot methanol-chloroform (1:1), and the total filtrate was evaporated under reduced pressure to give 16α-*hydroxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**7**) (1.38 g, 74%), m.p. 245-248°C (from ethyl acetate) (Found: M^+, 340. $C_{22}H_{28}O_3$ requires M, 340). The limited solubility of the diol in most solvents precluded full characterisation.

Acetic anhydride (0.25 cm^3, 2.6 mmol) was added to a stirred suspension of the diol (**7**) (76 mg, 0.22 mmol) in pyridine (1 cm^3). The mixture was stirred at 25°C for 2.5 h, during which time the suspended material dissolved. The mixture was poured into water and extracted with chloroform. The extract was washed with saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$), and the solvent evaporated under reduced pressure, to yield an oily residue (110 mg). Chromatography on silica gel (10 g) using ethyl acetate-toluene (1:9) as eluent gave 16α-*acetoxymethyl*-3-*methoxy*-14,17α-

ethenoestra-1,3,5(10)-*trien*-17β-*ol* (**8**) (75 mg, 88%), m.p. 123-125°C (from acetone-hexane); $[\alpha]_D$ +131° (*c* 1.0); ν_{max} 3594 (OH) and 1728 (OAc) cm^{-1}; δ_H (200 MHz) 0.95 (3H, d, *J* 0.9 Hz, 13β-Me), 2.06 (3H, s, 16^1-OAc), 2.78-2.88 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.95 (1H, dd, *J* 10.7 and 6.9 Hz, 16^1-H), 4.04 (1H, dd, *J* 10.7 and 8 Hz, 16^1-H), 5.88 and 6.05 (each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.6 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 76.1; H, 7.9%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.9; H, 7.9%; M, 382).

b) Sodium borohydride (597 mg, 15.8 mmol) was added in small portions to a stirred suspension of the 16α-carbaldehyde (**2**) (2.0 g, 5.3 mmol) in absolute ethanol (200 cm^3) at 0°C under nitrogen. After 90 min, the reaction was complete (TLC) and brine was added. Extraction of the mixture into chloroform, followed by washing (saturated $NaHCO_3$, brine), drying ($MgSO_4$), and evaporation of the solvent, gave a residue (2.09 g) which was adsorbed on silica gel (200 g) and eluted with ethyl acetate-hexane (2:3) to yield the 17β-hydroxy-16^1-acetate (**8**) (460 mg, 23 %). This was followed by mixed fractions (168 mg) and 16α-*hydroxymethyl*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**9**) (1.02 g, 59 %), m.p. 165-170°C (from acetone-hexane); $[\alpha]_D$ +91° (*c* 1.0); ν_{max} 3607 (OH) and 1368 (OAc) cm^{-1} ; δ_H (200 MHz) 0.99 (3H, s, 13β-Me), 2.11 (3H, s, 17β-OAc), 2.39-2.52 (1H, m, 9α-H), 2.8-2.88 (2H, m, 6-H_2), 3.36 (1H, ddd, *J* 11.5, 8.5 and 5.4 Hz, 16^1-H), 3.58 (1H, dd, *J* 11.5, 8.4 and 4.4 Hz, 16^1-H), 3.76 (3H, s, 3-OMe), 6.05 and 6.37 (each 1H, d, *J* 6.4 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.19 (1H, d, *J* 8.7 Hz, 1-H) (Found: C, 76.0; H, 7.7%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.9; H, 7.9%; M, 382).

Hydride Reductions of the Dihydro Cycloadduct (**5**)

a) Lithium aluminium hydride (320 mg, 8.5 mmol) was added in small portions to a stirred solution of the dihydro compound (**5**) (645 mg, 1.7 mmol) in dry tetrahydrofuran (50 cm^3) at 0°C under nitrogen. The mixture was stirred at 20°C for 20 min, then cooled to 0°C, and a saturated aqueous sodium sulfate solution was added dropwise until a flocculent white precipitate formed. Stirring was continued for 30 min, prior to filtering. The filter pad was rinsed repeatedly with chloroform-methanol (20:1), and the filtrate was concentrated under reduced pressure to yield 16α-*hydroxymethyl*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**10**) (520 mg, 90%), m.p. 220-223°C (Found: C, 77.25; H, 8.9%; M^+, 342. $C_{22}H_{30}O_3$ requires C, 77.15; H, 8.8%; M, 342). Insolubility in common solvents precluded full spectroscopic characterisation.

b) Sodium borohydride (71 mg, 1.9 mmol) was added in small portions to a solution of the 14α,17α-ethano 16α-carbaldehyde (**5**) (239 mg, 0.63 mmol) in ethanol (24 cm^3) at 0°C under nitrogen. After 60 min, the mixture was poured into saturated aqueous ammonium chloride and well shaken. The resulting suspension was vacuum filtered, and the precipitate (282 mg) was oven dried overnight, then adsorbed onto silica gel (28 g). Elution with ethyl acetate-toluene (1:3) yielded mixed fractions (8 mg) and 16α-*hydroxymethyl*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien* 17β-*yl acetate* (**11**) (200 mg, 83%), m.p. 144-146°C (from acetone-hexane); $[\alpha]_D$ +18° (*c* 1.2); ν_{max} 3409 (OH) and 1706 (OAc) cm^{-1}; δ_H (200 MHz) 1.02 (3H, d, *J* 0.6 Hz, 13β-Me), 2.06 (3H, s, 17β-OAc), 2.78-2.86 (2H, m, 6-H_2), 3.57 (1H, dd, *J* 12.1 and 5.1 Hz, 16^1-H), 3.76 (3H, s, 3-OMe), 3.88 (1H, dd, *J* 12.1 and 9.5 Hz, 16^1-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.2; H, 8.4%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; M, 384).

Preparation of 16^1-Tosylates

a) Toluene-*p*-sulfonyl chloride (1.55 g, 8.1 mmol) was added to a suspension of the diol (**7**) (921 mg, 2.7 mmol) in dry pyridine (30 cm^3) at 0°C. The mixture was stirred at 0°C for 15 min, then kept at 7°C for 37 h, whereupon the reaction was complete (TLC). Water was added and the mixture was acidified with aqueous 3M-hydrochloric acid prior to extraction with toluene. The organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure, to yield a colourless, crystalline residue (1.225 g), which was subjected to flash chromatography on silica gel (61 g). Elution with ethyl acetate-hexane (1:2) gave 3-*methoxy*-16α-*toluene*-p-*sulfonyloxymethyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**12**) (1.2 g, 85%), m.p. 141-144°C (from acetone-hexane); $[\alpha]_D$ +126° (*c* 1.0); ν_{max} 3599 (OH), 1359 and 1174 (OTs) cm^{-1}; δ_H (200 MHz) 0.91 (3H, s, 13β-Me), 2.38 (3H, s, 4'-Me), 2.5 obsc (1H, qd, *J* 3 x 7.9 and 4.4 Hz, 16β-H), 2.72-2.81 (2H, m, 6-H_2), 3.7 (3H, s, 3-OMe), 3.83 and 3.99 (each 1H, dd, *J* 9.4 and 7.9 Hz, 16^1-H_2), 5.7 and 6.01 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.55 (1H, d, *J* 2.7 Hz, 4-H), 6.63 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.19 (1H, d, *J* 8.7 Hz, 1-H), 7.35 (2H, d, *J* 8.6 Hz, 3'- and 5'-H) and 7.8 (2H, d, *J* 8.6 Hz, 2'- and 6'-H) (Found: C, 70.1; H, 6.9%; M^+, 494. $C_{29}H_{34}O_5S$ requires C, 70.4; H, 6.9%; M, 494).

b) Treatment of the 16^1-hydroxy 17β-acetate (**9**) (300 mg, 0.8 mmol) with toluene-*p*-sulfonyl chloride (446 mg, 2.3 mmol) in dry pyridine (8 cm^3) at 7°C for 40 h followed by work-up, as described in the foregoing experiment, gave a solid product (413 mg). Flash chromatography on silica gel (10 g) with toluene as eluent yielded 3-*methoxy*-16α-

toluene-p-*sulfonyloxymethyl*-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**13**) (388 mg, 93%), m.p. 125-126°C (from acetone-hexane); $[\alpha]_D$ +86° (*c* 1.0); ν_{max} 1734 (OAc), 1365 and 1173 (OTs) cm^{-1}; δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 2.07 (3H, s, 17β-OAc), 2.46 (3H, s, 4'-Me), 2.8-2.89 (2H, m, 6-H_2), 3.76 obsc (1H, dd, *J* 9.4 and 3.4 Hz, 16^1-H), 3.77 (3H, s, 3-OMe), 4.18 (1H, dd, *J* 9.4 and 6.1 Hz, 16^1-H), 6.01 and 6.17 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.5 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.5 Hz, 2-H), 7.19 (1H, d, *J* 8.6 Hz, 1-H), 7.35 (2H, d, *J* 8.3 Hz, 3'- and 5'-H) and 7.78 (2H, d, *J* 8.3 Hz, 2'- and 6'-H) (Found: C, 69.2; H, 6.8%; M^+, 536. $C_{31}H_{36}O_6S$ requires C, 69.4; H, 6.8%; M, 536).

c) The 16^1,17β-diol (**10**) (900 mg, 4.6 mmol) was tosylated as in the foregoing experiments, and the product (749 mg) (isolated by work-up into toluene) was flash chromatographed on silica gel (98 g) with ethyl acetate-hexane (2:3) as eluent, to give 3-*methoxy*-16α-*toluene*-p-*sulfonyloxymethyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**14**) as a non-crystalline product (400 mg, 54%), ν_{max} 3596 (OH) and 1360 (OTs) cm^{-1}; δ_H (200 MHz) 0.89 (3H, s, 13β-Me), 2.35 (1H, m, 16β-H), 2.44 (3H, s, 4'-Me), 2.48-2.64 (1H, m, 9α-H), 2.77-2.84 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 4.18 (1H, dd, *J* 9.4 and 7.8 Hz, 16^1-H), 4.24 (1H, dd, *J* 9.4 and 7.5 Hz, 16^1-H), 6.6 (1H, d, *J* 2.7 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.19 (1H, d, *J* 8.6 Hz, 1-H), 7.35 (2H, d, *J* 8.1 Hz, 3'- and 5'-H) and 7.8 (2H, d, *J* 8.1 Hz, 2'- and 6'-H) (Found: C, 69.8; H, 7.2%; M^+, 496. $C_{29}H_{36}O_5S$ requires C, 70.1; H, 7.3%; M, 496).

d) Tosylation of the 16^1-hydroxy 17β-acetate (**11**) (548 mg, 1.4 mmol), followed by work-up (toluene), in a similar manner to that described in the foregoing experiments gave rise to an oily residue (619 mg), which was flash chromatographed on silica gel (73 g). Elution with ethyl acetate-toluene (1:5) yielded 3-*methoxy*-16α-*toluene*-p-*sulfonyloxymethyl*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*yl acetate* (**15**) as a non-crystalline product (235 mg, 31%), ν_{max} 1727 (OAc) and 1365 and 1171 (OTs) cm^{-1}; δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 1.96 (3H, s, 17β-OAc), 2.44 (3H, s, 4'-Me), 2.77-2.86 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 4.14 (1H, t, *J* 2 x 9.9 Hz, 16^1-H), 4.52 (1H, dd, *J* 9.9 and 4.8 Hz, 16^1-H), 6.6 (1H, d, *J* 2.6 Hz, 4-H), 6.68 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.18 (1H, d, *J* 8.6 Hz, 1-H), 7.34 (2H, d, *J* 8.1 Hz, 3'- and 5'-H) and 7.79 (2H, d, *J* 8.1 Hz, 2'- and 6'-H) (Found: M^+-TsOH, 366. $C_{31}H_{38}O_6S$ requires M, 538. M-TsOH, 366).

This was followed by 16α-*acetoxymethyl*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-*ol* (**16**) (349 mg, 65%), m.p. 123-126°C (from chloroform-methanol); $[\alpha]_D$ +31° (*c* 0.8); ν_{max} 3597 (OH) and 1727 (OAc) cm^{-1}; δ_H (200 MHz) 0.96 (3H, s, 13β-Me) and 2.07 (3H, s, 16^1-OAc), 2.54-2.68 (1H, m, 9α-H), 2.79-2.88 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.27 (2H, dd, *J* 7.7 and 1.8 Hz, 16^1-H_2), 6.62 (1H, d, *J* 2.8 Hz,

4-H), 6.74 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.23 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 75.2; H, 8.5%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; M, 384).

14-*Allyl*-3-*methoxy*-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**17**)

a) Methanolic M-potassium hydroxide (11 cm^3, 11 mmol) was added to a stirred solution of the 17β-hydroxy 16^1-tosylate (**12**) (1.812 g, 3.7 mmol) in methanol (65 cm^3) at 20°C under nitrogen. After 1 h the reaction was complete (TLC). Water was added and the mixture was acidified with aqueous 3M-hydrochloric acid and extracted with chloroform. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated under reduced pressure, to yield an oily residue (1.3 g) which was flash chromatographed on silica gel (65 g). Elution with ethyl acetate-toluene (1:24) gave the 14β-*allyl enone* (**17**) (1.18 g, 100%), m.p. 61-63°C (from diisopropyl ether); $[\alpha]_D$ +216° (*c* 1.0); ν_{max} 1701 (CO) and 1640 (C:C) cm^{-1}; λ_{max} 325 (ε 233) and 245 (ε 10395) nm; δ_H (400 MHz) 1.12 (3H, s, 13β-Me), 1.26 (1H, m, 7α-H), 1.35 (1H, m, 11β-H), 1.56 (1H, dt, *J* 13.8 and 2 x 7.9 Hz, 12α-H), 1.86 (1H, m, 12β-H), 1.91 (1H, m, 8β-H), 2.17 (1H, dq, *J* 12.4 and 2 x 2.4 Hz, 7β-H), 2.26 obsc (1H, m, 11α-H), 2.31 obsc (1H, m, 9α-H), 2.44 (1H, ddt, *J* 15, 5.9 Hz and 2 x 1.5 Hz, 14^1-$H_{pro\mathit{S}}$), 2.56 (1H, dd, *J* 15 and 8.5 Hz, 14^1-$H_{pro\mathit{R}}$), 2.75 (2H, dd, *J* 8.4 and 3.6 Hz, 6-H_2), 3.74 (3H, s, 3-OMe), 5.13 (1H, br d, $W_{1/2}$ 7 Hz, 14^3-*Z*-H), 5.16 (1H, ddd, *J* 10.2, 3.2 and 1.5 Hz, 14^3-*E*-H), 5.82 (1H, dddd, *J* 16.8, 10.2, 8.5 and 5.9 Hz, 14^2-H), 6.20 (1H, d, *J* 5.8 Hz, 16-H), 6.55 (1H, d, *J* 2.7 Hz, 4-H), 6.68 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.04 (1H, d, *J* 8.7 Hz, 1-H), 7.31 (1H, d, *J* 5.8 Hz, 15-H); δ_C (100 MHz) 216.1 (s, C-17), 165.4 (d, C-16), 157.3 (s, C-3), 137.1 (s, C-5), 134 (d, C-14^2), 133.1 (s, C-10), 131.4 (s, C-16), 128.1 (d, C-1), 118.7 (t, C-14^3), 113.0 (d, C-4), 112.3 (d, C-2), 55.2 (q, 3-OMe), 54.2 and 52.2 (each s, C-13 and C-14), 41.6 (d, C-8), 38.3 (t, C-14^1), 34.2 (d, C-9), 30.7 (t, C-6), 30.3 (t, C-12), 27.9 (t, C-11), 24.2 (t, C-7) and 21.6 (q, C-18) (Found: C, 82.1; H, 8.4%; M^+, 322. $C_{22}H_{26}O_2$ requires C, 82.0; H, 8.1%; M, 322).

b) Similar alkaline treatment of the 17β-acetoxy 16^1-tosylate (**13**) (600 mg, 1.1 mmol) was incomplete after 1h at 20°C, but a further reaction period of 1 h at 55°C and isolation and chromatography as in the foregoing experiment gave the product (**17**) (361 mg, 100%).

c) 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.3 cm^3, 2.02 mmol) was added to a stirred solution of hydroxy tosylate (**12**) (100 mg, 0.2 mmol) in tetrahydrofuran (2 cm^3). The mixture was stirred at 25°C for 26 h, then diluted with dichloromethane. The solution was

added to a separating funnel containing 0.1M-hydrochloric acid (15 cm^3), and the product was isolated by extraction into dichloromethane. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield the allyl enone (**17**) as a colourless oil (61 mg, 97%).

14-*Allyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**18**)

Ethereal 5% methyllithium (0.54 cm^3, 1.2 mmol) was added to a stirred suspension of copper(I) iodide (237 mg, 1.2 mmol) in dry tetrahydrofuran (15 cm^3) at 0°C under nitrogen. The resultant suspension of methylcopper was cooled to -78°C, and hexamethylphosphoric triamide (2.7 cm^3, 15.5 mmol) and a 20% hexane solution of diisobutylaluminium hydride (11 cm^3, 15.5 mmol) were added successively. The reaction mixture was stirred at -78°C for 30 min, and then the allyl enone (**17**) (1 g, 3.1 mmol) in dry tetrahydrofuran (3.5 cm^3) was added, and the mixture was stirred at -78°C for 1 h. Aqueous 0.5M-hydrochloric acid (10 cm^3) was added, and the mixture was extracted with toluene. The extract was washed successively with M-hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, then dried ($MgSO_4$), and concentrated under reduced pressure to yield a solid residue (1.04 g) which was flash chromatographed on silica gel (50 g). Elution with ethyl acetate-toluene (1:19) gave the *allyl ketone* (**18**) (919 mg, 91%), m.p. 75-78°C (from acetone-methanol); $[\alpha]_D$ +81° (*c* 1.0); ν_{max} 1725 (CO) cm^{-1}; δ_H 1.11 (3H, d, *J* 0.8 Hz, 13β-Me), 2.13 (1H, m, 14^1-H), 2.27 (1H, dd, *J* 19.2 and 9.4 Hz, 16α-H), 2.33 (1H, m, 14^1-H), 2.42-2.52 (1H, m, 16β-H), 2.6-2.68 (1H, m, 9α-H), 2.83-2.88 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.03 (H, ddt, *J* 10 and 4 x 1.1 Hz, 14^3-*Z*-H), 5.13 (1H, ddd, *J* 16.8, 3.5 and 2 x 1.5 Hz, 14^3-*E*-H), 5.78 (1H, dddt, *J* 16.8, 10 and 2 x 7.4 Hz, 14^2-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.19 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 219.2 (s, C-17), 157.7 (s, C-3), 137.9 (s, C-5), 135.3 (d, $C\text{-}14^2$), 132.5 (s, C-10), 126.4 (d, C-1), 118.1 (t, $C\text{-}14^3$), 113.6 (d, C-4), 111.7 (d, C-2), 55.2 (q, 3-OMe), 52.8 (s, C-14), 47.6 (s, C-13), 42.8 (t, $C\text{-}14^1$), 42.3 (d, C-8), 38.0 (d, C-9), 33.8 (d, C-16), 33.0 (t, C-12), 30.4 (t, C-6), 25.6 (t, C-11), 24.8 (t, C-15), 23.5 (t, C-7) and 15.5 (q, C-18) (Found: C, 81.5; H, 8.5%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; M, 324). This was followed by a small amount of unreacted material (85 mg).

b) Methanolic M-potassium hydroxide (2.2 cm^3, 2.2 mmol) was added to a stirred solution of the 14,17α-ethano 17β-hydroxy 16^1-tosylate (**14**) (362 mg, 0.73 mmol) in methanol (9 cm^3) at 20°C under nitrogen. After 16 h, a further aliquot of methanolic base (2 cm^3, 2 mmol) was added, and the temperature was elevated to 50°C. After a further

3 h, the reaction was complete (TLC). The mixture was acidified with aqueous 3M-hydrochloric acid and extracted with toluene. The organic layer was washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate, and evaporated under reduced pressure, yielding a non-crystalline residue (296 mg) which was chromatographed on silica gel (24 g) using ethyl acetate-toluene (1:99) as eluent. This gave the allyl ketone (**18**) (237 mg, 100 %).

c) 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.6 cm^3, 4.02 mmol) was added to a stirred solution of the hydroxy tosylate (**14**) (290 mg, 0.57 mmol) in toluene (11 cm^3). The mixture was refluxed under nitrogen for 26 h, then diluted with dichloromethane. The solution was added to a separating funnel containing 0.1M-hydrochloric acid (15 cm^3), and the product was isolated by extraction into dichloromethane. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent removed under reduced pressure to yield the allyl ketone (**18**) (204 mg, 100%).

14-*Acetonyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**19**)

Palladium(II) chloride (142 mg, 0.8 mmol) and copper(I) chloride (395 mg, 3.99 mmol) were mixed in dimethylformamide (37 cm^3) and water (3.7 cm^3) and stirred vigorously at 20°C under an oxygen atmosphere. After 2.5 h, the allyl ketone (**18**) (0.5 g, 1.54 mmol) was added and the mixture was heated to 65°C. After 5 h, the mixture was poured into water and extracted with toluene. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to dryness to yield a yellow oil (627 mg), which was chromatographed on silica gel (55 g) using ethyl acetate-toluene (1:9) as eluent. Starting material (22 mg, 4%) eluted first, followed by non-steroidal material (191 mg), and then the *diketone* (**19**) (363 mg, 69%) as an oil, $[\alpha]_D$ +8° (*c* 0.8); ν_{max} 1726br (CO) cm^{-1}; δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 2.15 (3H, s, 14^3-Me), 2.39 and 2.62 (each 1H, d, *J* 17.2 Hz, 14^1-H_2), 2.83-2.91 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 340.203. $C_{22}H_{28}O_3$ requires M, 340.204).

17α-*Hydroxy*-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17^2-*one* (**21**)

Methanolic M-potassium hydroxide (5.5 cm^3, 5.5 mmol) was added to a stirred solution of the diketone (**19**) (470 mg, 1.38 mmol) in tetrahydrofuran (17 cm^3) at 20°C under nitrogen. After 30 min, the reaction was complete (TLC), and water was added. The

mixture was acidified with aqueous 2M-hydrochloric acid (3 cm^3) and extracted with toluene. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield a crystalline residue (420 mg) which was chromatographed on silica gel (21 g). Elution with ethyl acetate-toluene (2:3) yielded an isomeric mixture (*ca* 1:2 from NMR) formulated as the $16^1\xi$-hydroxy-$16^1\xi$-methyl-3-methoxy-14,16β-ethano-14β-estra-1,3,5(10)-trien-17-ones (**20a** and **20b**) (27 mg, 6%), ν_{max} 3584 (OH) and 1733 (CO) cm^{-1}; δ_H (200 MHz) 1.04 (3H, s, 13β-Me) and 1.35 (3H, s, 16^1-Me) (minor component), 1.16 (3H, s, 13β-Me) and 1.45 (3H, s, 16^1-Me) (major component), 2.84-2.93 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.9 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.9 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 340.204. $C_{22}H_{28}O_3$ requires M, 340.203).

This was followed by mixed fractions (49 mg) and then by the *hydroxy ketone* (**21**) (327 mg, 70%), m.p. 215-217°C (from dichloromethane-methanol); $[\alpha]_D$ +11° (*c* 1.0); ν_{max} 3596 (OH) and 1707 (CO) cm^{-1}; δ_H (400 MHz) 1.06 (3H, s, 13β-Me), 1.5 (1H, qd, *J* 3 x 12.3 and 4.7 Hz), 2.04 (1H, qt, *J* 4 x 13.1 and 2 x 3.6 Hz), 2.2 (1H, dd, *J* 17.4 and 2.6 Hz, 17^3α-H), 2.4 (1H, dq, *J* 13.4 and 3 x 3.8 Hz, 11α-H), 2.49 (1H, dd, *J* 17.4 and 2 Hz, 17^1α-H), 2.51 (1H, dd, *J* 17.4 and 2 Hz, 17^3β-H), 2.63 (1H, td, *J* 2 x 14.6 and 3.8 Hz, 9α-H), 2.8 obsc (1H, dd, *J* 17.4 and 2.8 Hz, 17^1β-H), 2.8-2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.24 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 209.7 (s, C-17^2), 157.6 (s, C-3), 137.6 (s, C-5), 132.4 (s, C-10), 126.5 (d, C-1), 113.5 (d, C-4), 111.8 (d, C-2), 81.2 (s, C-17), 55.2 (q, 3-OMe), 53.4 (t, C-17^1), 50.6 (t, C-17^3), 45.9 (s, C-13), 45.2 (s, C-14), 42.0 (d, C-8), 37.5 (d, C-9), 34.9 (t, C-16), 30.3 (t, C-6), 28.9 (t, C-12), 26.0 (t, C-15), 25.8 (t, C-11), 23.3 (t, C-7) and 13.5 (q, C-18) (Found: C, 77.4; H, 8.4%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; M, 340).

17^2,17^2-*Ethylenedithio*-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**22**)

a) A solution of the hydroxy ketone (**21**) (500 mg, 1.45 mmol) in dichloromethane (20 cm^3) was added to a well-stirred mixture of ethane-1,2-dithiol (0.5 cm^3, 6 mmol) and zinc trifluoromethanesulfonate (1.05 g, 2.9 mmol) in dichloromethane (20 cm^3). The mixture was stirred at 20°C under nitrogen for 3.5 h. Thereafter, water was added followed by solid sodium hydrogen carbonate to neutralise the mixture. The mixture was extracted with chloroform; the organic phase was washed with saturated sodium hydrogen carbonate and brine, and dried over magnesium sulfate, then evaporated under reduced pressure. The colourless foam (660 mg) was chromatographed on silica gel

(65 g) using ethyl acetate-toluene (1:9) as eluent to give the *hydroxy* 17^2,17^2-*dithioketal* (**22**) (510 mg, 85%), m.p. 86-90°C (from chloroform-methanol); $[\alpha]_D$ +8° (*c* 1.0); ν_{max} 3598 (OH) cm^{-1}; δ_H (200 MHz) 0.94 (3H, s 13β-Me), 2.16 and 2.46 (each 1H, d, *J* 14.9 Hz, 17^3-H_2), 2.34 and 2.7 (each 1H, d, *J* 13.9 Hz, 17^1-H_2), 2.78-2.83 (2H, m, 6-H_2), 3.24-3.46 (4H, m, -SCH_2CH_2S-), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.24 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 416.184. $C_{24}H_{32}O_2S_2$ requires M, 416.184).

b) Ethane-1,2-dithiol (0.5 cm^3, 6 mmol) and a solution of toluene-*p*-sulfonic acid (30 mg, 0.15 mmol) in glacial acetic acid (1 cm^3) were added successively to a stirred solution of the hydroxy ketone (**21**) (100 mg, 0.29 mmol) in acetic acid (4 cm^3). The mixture was stirred under nitrogen at 20°C for 8 h, whereupon it was poured onto water. Solid sodium hydrogen carbonate was added slowly until the mixture was neutral. The slurry was subjected to work-up (chloroform), yielding a colourless foam (130 mg) which was chromatographed as above to give the dithioketal (**22**) (104 mg, 85%).

3-*Methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**23**)

Raney nickel (Aldrich, W2, 1 g) was washed (3x) with absolute ethanol, the ethanol was decanted, and the reagent was covered with further ethanol (10 cm^3). The dithioketal (**22**) (268 mg, 0.64 mmol) was added and the mixture was heated to reflux under nitrogen with vigorous stirring. After 3 h, the mixture was filtered through Celite, which was then thoroughly rinsed with toluene. The filtrate was concentrated under reduced pressure to yield a crystalline residue (200 mg) which was redissolved in toluene. The solution was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The solid residue (199 mg, 95 %) was recrystallised from chloroform-methanol to yield the 14β,17β-*propano compound* (**23**), m.p. 155-156°C; $[\alpha]_D$ +8° (*c* 1.0); ν_{max} 3596 (OH) cm^{-1}; δ_H (200 MHz) 0.91 (3H, s, 13β-Me), 2.31 (1H, dq, *J* 12.6 and 3 x 3.6 Hz, 11α-H), 2.6 (1H, br td, *J* 2 x 11.3 and 3.6 Hz, 9α-H), 2.76-2.83 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.24 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.4 (s, C-3), 138.0 (s, C-5), 133.6 (s, C-10), 126.3 (d, C-1), 113.4 (d, C-4), 111.4 (d, C-2), 82.0 (s, C-17), 55.2 (q, 3-OMe), 46.9 (s, C-13), 45.2 (s, C-14), 41.9 (d, C-8), 37.5 (d, C-9), 34.5 (t, C-16), 34.2 (t, C-17^1), 30.6 (t, C-12), 30.2 (t, C-6), 29.2 (t, C-17^3), 25.9 (t, C-15), 25.2 (t, C-11), 23.7 (t, C-7), 18.8 (t, C-17^2) and 13.4 (q, C-18) (Found: C, 81.1; H, 9.4%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; M, 326).

14,17β-*Propano*-14β-*estra*-1,3,5(10)-*trien*-3,17α-*diol* (**24**)

Diisobutylaluminium hydride (1.5M solution in toluene, 3.2 cm^3, 4.8 mmol) was added to a stirred solution of the alcohol (**23**) (155 mg, 0.47 mmol) in toluene (31 cm^3), and the mixture was refluxed under nitrogen for 24 h. Saturated aqueous ammonium chloride was added, followed by water. The mixture was acidified with dilute acetic acid and a pale yellow crystalline residue (143 mg, 97%) was isolated by extraction with ethyl acetate. This material was filtered through alumina (Merck Act. III, 5 g) with ethyl acetate. Recrystallisation of the colourless material (140 mg) from ethyl acetate yielded the 3,17α-*diol* (**24**) (83 mg, 57 %), m.p. 270-271°C; $[\alpha]_D$ +9° (*c* 1.0, THF) (Found: C, 80.5; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; M, 312).

Reduction of the 17α-*Hydroxy* 17^2-*Ketone* (**21**)

Lithium aluminium hydride (111 mg, 2.9 mmol) was added in small portions to a stirred solution of the hydroxy ketone (**21**) (200 mg, 0.59 mmol) in tetrahydrofuran (14 cm^3) at 0°C and the mixture was stirred at 0°C for 1 h. Saturated aqueous ammonium chloride was added, excess tetrahydrofuran was removed under reduced pressure, and the mixture was extracted with ethyl acetate. The extract was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield a colourless oil (200 mg). This residue was chromatographed on silica gel (20 g) using ethyl acetate-toluene (7:13) to give (17^2R)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^2-*diol* (**25**) (70 mg, 35%), m.p. 179-182°C (from chloroform-hexane); $[\alpha]_D$ +9° (*c* 1.0); ν_{max} 3602 (OH) cm^{-1}; δ_H (200 MHz) 0.82 (3H, s, 13β-Me), 2.55-2.69 (1H, br td, 9α-H), 2.76-2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.27 (1H, t, *J* 2 x 6.2 Hz, 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.23 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 133.4 (s, C-10), 126.4 (d, C-1), 113.5 (d, C-4), 111.6 (d, C-2), 80.8 (s, C-17), 66.3 (d, C-17^2), 55.2 (q, 3-OMe), 48.4 (s, C-13), 46.2 (s, C-14), 44.4 (d, 17^1), 42.2 (d, C-8), 41.0 (t, C-17^3), 36.9 (d, C-9), 34.0 (t, C-16), 30.5 (t, C-6), 28.6 (t, C-12), 25.9 (t, C-15), 24.6 (t, C-11), 23.5 (t, C-7) and 13.5 (q, C-18) (Found: C, 77.3; H, 9.0%; M^+, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; M, 342).

This was followed by (17^2S)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^2-*diol* (**26**) (113 mg, 56%), m.p. 185-188°C (from ethyl acetate); $[\alpha]_D$ +5° (*c* 1.0); ν_{max} 3601 (OH) cm^{-1}; δ_H (200 MHz) 0.97 (3H, s, 13β-Me), 2.32 (1H, dq, *J* 13.2 and 3 x 4 Hz, 11α-H), 2.53-2.66 (1H, br td, 9α-H), 2.77-2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.04 (1H, tt, *J* 2 x 10.5 and 2 x 7.4 Hz, 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72

(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 133.3 (s, C-10), 126.3 (d, C-1), 113.5 (d, C-4), 111.6 (d, C-2), 81.0 (s, C-17), 66.0 (d, C-17^2), 55.2 (q, 3-OMe), 45.9 and 45.1 (each s, C-13 and C-14), 44.1 (t, C-17^1), 41.6 (d, C-8), 40.0 (t, C-17^3), 37.3 (d, C-9), 34.3 (t, C-16), 30.5 (t, C-6), 28.8 (t, C-12), 25.8 (t, C-15), 25.2 (t, C-11) 23.8 (t, C-7) and 13.7 (q, C-18) (Found: C, 77.0; H, 8.95%; M$^+$, 342. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%; M, 342).

Deprotection of the 3-Methyl Ethers (**25**) *and* (**26**)

a) Diisobutylaluminium hydride (DIBAL) (1.5M solution in toluene, 1.95 cm^3, 2.9 mmol) was added to a stirred solution of the diol (**25**) (100 mg, 0.3 mmol) in toluene (20 cm^3), and the mixture was refluxed under nitrogen for 25 h. Thereafter, further DIBAL (1 cm^3, 1.5 mmol) was added and the mixture heated to reflux for another 16 h. The mixture was cooled to 20°C and saturated aqueous ammonium chloride was carefully added, followed by water. The mixture was acidified with dilute acetic acid and extracted with ethyl acetate. The extract was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the solid residue (93 mg) on silica gel (10 g) using ethyl acetate as eluent gave, in order of elution, mixed fractions (23 mg) of starting material and product, followed by (17^{2}R)-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-3,17α,17^2-*triol* (**27**) (67 mg, 68 %), m.p. 277-280°C (from ethyl acetate); $[\alpha]_D$ -21° (*c* 1.0, pyridine) (Found: C, 76.6; H, 8.6%; M$^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; M, 328).

b) Similar treatment of the diol (**26**) (100 mg, 0.3 mmol) - only one addition of DIBAL, and a total reaction time of 25 h being required this time, however - followed by chromatography of the residue (94 mg) on silica gel (10 g) with ethyl acetate-toluene (1:1) as eluent, gave (17^{2}S)-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-3,17α,17^2-*triol* (**28**) (75 mg, 76%), m.p. 251-253°C (from acetone-hexane); $[\alpha]_D$ -2° (*c* 0.5, pyridine) (Found: C, 77.1; H, 8.5%; M$^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; M, 328).

Formation of the 17^2-*Tosylhydrazones* (**29**)

a) Trifluoroacetic acid (0.016 cm^3) was added to a stirred mixture of toluene-*p*-sulfonohydrazide (81 mg, 0.45 mmol) and the hydroxy ketone (**21**) (50 mg, 0.15 mmol) in tetrahydrofuran (5 cm^3) at 20°C under nitrogen. After 16 h, saturated aqueous sodium hydrogen carbonate was added. Extraction of the mixture with chloroform, and

successive washing (saturated $NaHCO_3$, brine), drying ($MgSO_4$), and evaporation of the organic phase, gave a colourless oil (149 mg) which was chromatographed on silica gel (15 g). Elution with ethyl acetate-toluene (3:7) yielded 17α-*hydroxy*-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17^2-*one toluene*-p-*sulfonylhydrazone* (**29a** and **29b**) as separable *syn*- and *anti*- isomers. Isomer (**29a**) (49 mg, 64%) eluted first, m.p. 154-158°C (from chloroform-methanol); $[\alpha]_D$ -3° (*c* 1.0); ν_{max} 3599 (OH), 3290 and 3216 (NH), and 1336 and 1162 (SO_2N) cm^{-1}; δ_H (200 MHz) 0.85 (3H, s, 13β-Me), 2.41 (3H, s, Ar-CH_3), 2.72-2.82 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 6.59 (1H, d, *J* 2 Hz, 4-H), 6.69 (1H, dd, *J* 8.6 and 2 Hz, 2-H), 7.18 (1H, d, *J* 8.6 Hz, 1-H), 7.3 (2H, d, *J* 8.2 Hz, 3'- and 5'-H) and 7.79 (2H, d, *J* 8.2 Hz, 2'- and 6'-H) (Found: M^+, 508.238. $C_{29}H_{36}N_2O_4S$ requires M, 508.239).

Second to elute was isomer (**29b**) (27 mg, 36%), m.p. 177-180°C (from acetone-hexane); $[\alpha]_D$ -24° (*c* 1.0); ν_{max} 3599 (OH), 3292 and 3201 (NH), and 1336 and 1163 (SO_2N) cm^{-1}; δ_H (200 MHz) 0.89 (3H, s, 13β-Me), 2.42 (3H, s, Ar-CH_3), 2.75-2.85 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.9 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.9 Hz, 2-H), 7.21 (1H, d, *J* 8.6 Hz, 1-H), 7.32 (2H, d, *J* 8.2 Hz, 3'- and 5'-H) and 7.84 (2H, d, *J* 8.2 Hz, 2'- and 6'-H) (Found: M^+, 508.239. $C_{29}H_{36}N_2O_4S$ requires M, 508.239).

b) Toluene-*p*-sulfonohydrazide (81 mg, 0.45 mmol) was added to a stirred solution of the hydroxy ketone (**21**) (50 mg, 0.15 mmol) in glacial acetic acid (3 cm^3) at 20°C under nitrogen. The mixture was stirred for 23 h at 30°C, then added to water, and solid sodium hydrogen carbonate was added slowly until the mixture was neutral. A similar work-up (chloroform) to that described above gave an opaque oil (138 mg), which was chromatographed on silica gel (14 g) using ethyl acetate-toluene (3:7) to yield the tosylhydrazones (**29a**) (42 mg, 55%) and (**29b**) (34 mg, 45%).

c) Toluene-*p*-sulfonic acid (30 mg, 0.15 mmol) was added to a stirred solution of the hydroxy ketone (**21**) (500 mg, 1.5 mmol) and toluene-*p*-sulfonohydrazide (810 mg, 4.5 mmol) in absolute ethanol (50 cm^3), and the mixture was refluxed for 2.5 h under nitrogen. The mixture was cooled to 20°C, water was added, and the two isomeric tosylhydrazones (**29a** and **29b**) (1.4 g) were isolated by work-up (chloroform), as described in (a). The products were not separated.

Elimination of the Tosylhydrazones (**29a**) *and* (**29b**)

n-Butyllithium (1.5M in hexane, 2.5 cm^3, 3.75 mmol) was added to a stirred solution of a mixture of the tosylhydrazones (**29a** and **29b**) (380 mg, 0.75 mmol) in tetrahydrofuran

(25 cm^3) at 0°C under nitrogen. After stirring for 1.5 h at 0°C, further n-BuLi (2.5 cm^3) was added and the mixture was kept at 0°C for another 1.5 h. Water was added, followed by aqueous 3M-hydrochloric acid, and the products were extracted into toluene. The organic layer was washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate, and the solvent removed under reduced pressure to give an opaque oil (450 mg), which was chromatographed on silica gel (68 g) using ethyl acetate-toluene (1:9). First to elute was 3-*methoxy*-14,17β-*prop*-17^1-*eno*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**30**) (75 mg, 31%), m.p. 112-114°C (from chloroform-methanol); $[\alpha]_D$ +2° (*c* 1.1); ν_{max} 3600 (OH) cm^{-1}; δ_H (200 MHz) 0.94 (3H, d, *J* 0.6 Hz, 13β-Me), 2.18 (1H, ddd, *J* 17.8, 3.9 and 1.5 Hz, 17^3-H), 2.34 (1H, dq, *J* 12.9 and 3 x 3.5 Hz, 11α-H), 2.46-2.61 (1H, br td, 9α-H), 2.76-2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.5 (1H, ddd, *J* 9.8, 3.9 and 2.6 Hz, 17^2-H), 5.75 (1H, ddd, *J* 9.8, 2.3 and 1.5 Hz, 17^1-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.24 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 136.9 (d, C-17^1), 133.0 (s, C-10), 126.6 (d, C-1), 123.8 (d, C-17^2), 113.5 (d, C-4), 111.7 (d, C-2), 82.3 (s, C-17), 55.2 (q, 3-OMe), 46.0 (s, C-13), 44.5 (s, C-14), 42.8 (d, C-8), 40.0 (t, C-16), 38.6 (t, C-17^3), 37.8 (d, C-9), 30.6 (t, C-6), 29.2 (t, C-12), 27.1 (t, C-15), 26.4 (t, C-11), 22.8 (t, C-7) and 14.0 (q, C-18) (Found: M^+, 324.209. $C_{22}H_{28}O_2$ requires M, 324.209).

Second to elute was 3-*methoxy*-14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**31**) (60 mg, 25%), m.p. 127-130°C (from chloroform-methanol); $[\alpha]_D$ -46° (*c* 0.8); ν_{max} 3600 (OH) cm^{-1}; δ_H (200 MHz) 0.91 (3H, s, 13β-Me), 2.59-2.72 (1H, br td, 9α-H), 2.82-2.88 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.51 (1H, ddd, *J* 9.6, 3.8 and 2.7 Hz, 17^2-H), 5.88 (1H, ddd, *J* 9.6, 2.2 and 2 Hz, 17^3-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.24 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.5 (s, C-3), 137.9 (s, C-5), 135.6 (d, C-17^3), 133.3 (s, C-10), 126.2 (d, C-1), 123.6 (d, C-17^2), 113.6 (d, C-4), 111.5 (d, C-2), 81.7 (s, C-17), 55.2 (q, 3-OMe), 49.6 (s, C-13), 44.7 (s, C-14), 42.5 (t, C-17^1), 38.9 (d, C-8), 37.4 (d, C-9), 36.3 (t, C-16), 30.5 (t, C-6), 30.3 (t, C-15), 27.8 (t, C-12), 25.6 (t, C-11), 23.8 (t, C-7) and 13.2 (q, C-18) (Found: M^+, 324.209. $C_{22}H_{28}O_2$ requires M, 324.209).

Deprotection of the 3-Methyl Ethers (**30**) *and* (**31**)

a) Diisobutylaluminium hydride (1.5M solution in toluene, 1.3 cm^3, 2.0 mmol) was added to a stirred solution of the olefinic alcohol (**30**) (65 mg, 0.2 mmol) in toluene (13 cm^3), and the mixture was refluxed under nitrogen for 25 h. Thereafter, the mixture was cooled to 20°C and saturated aqueous ammonium chloride was added, followed by water. The mixture was acidified with dilute acetic acid and extracted with ethyl acetate. The extract

was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated under reduced pressure to give a solid residue (64 mg). Flash chromatography on silica gel (7 g) using ethyl acetate-toluene (3:7) as eluent yielded 14,17β-*prop*-17^1-*eno*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**32**) (45 mg, 73%), m.p. 263-264°C (from ethyl acetate); $[\alpha]_D$ +5° (*c* 0.4, pyridine) (Found: C, 81.0; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; M, 310).

b) Similar treatment of the olefinic alcohol (**31**) (56 mg, 0.17 mmol), followed by flash chromatography of the product (53 mg) on silica gel (6 g) with ethyl acetate-toluene (3:7) as eluent, gave 14,17β-*prop*-17^2-*eno*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**33**) (45 mg, 70%), m.p. 273-274°C (from ethyl acetate); $[\alpha]_D$ -57° (*c* 0.5, pyridine) (Found: C, 81.0; H, 8.5; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; M, 310).

Hydroboration-Oxidation of the Allyl Ketone (**18**)

a) Borane-dimethyl sulfide (2.5 cm^3, 2.6 mmol) was added to a stirred solution of the allyl ketone (**18**) (1.2 g, 3.7 mmol) in tetrahydrofuran (90 cm^3) at 20°C under nitrogen. The mixture was refluxed for 2 h, whereupon all starting material had been consumed (TLC). The mixture was cooled to 0°C and aqueous 6M-sodium hydroxide (8 cm^3) was added slowly, followed by 30% hydrogen peroxide (6 cm^3). A white suspension formed, and the mixture was stirred at 40°C overnight. Thereafter, excess tetrahydrofuran was removed under reduced pressure, and the residue was poured into water and extracted with ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a crystalline residue (1.217 g) which was twice recrystallised from ethyl acetate to yield pure 3-*methoxy*-14-*(3-hydroxypropyl)*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**35**) (413 mg, 32%), m.p. 187-189°C; $[\alpha]_D$ +32° (*c* 1.0); ν_{max} 3611 (OH) cm^{-1}; δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 1.9 (1H, s, exch. by D_2O, OH), 2.46-2.62 (1H, br td, 9α-H), 2.76-2.86 (2H, m, 6-H_2), 3.55-3.61 (2H, m, 14^3-H_2), 3.76 (3H, s, 3-OMe), 4.21 (1H, dd, *J* 9.1 and 7 Hz, 17β-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.24 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 76.7; H, 9.4%; M^+, 344. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.4%; M, 344).

The mother liquor residues were combined (800 mg) and flash chromatographed on silica gel (80 g) using ethyl acetate-toluene (3:2) as eluent. First to elute was the non-crystalline hydroxy ketone (**34**) (25 mg, 2%); ν_{max} 3621 (OH) and 1726 (CO) cm^{-1}; δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 1.79 (1H, br. s, exch. by D_2O, 14^3-OH), 2.57-2.69 (1H, m, 9α-H), 2.81-2.9 (2H, m, 6-H_2), 3.57 (2H, t, *J* 2 x 6 Hz, 14^3-H_2), 3.77 (3H, s, 3-OMe),

6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 342.224. $C_{22}H_{30}O_3$ requires M, 342.224). This was followed by an inseparable mixture of the diols (**35** and **36**) (738 mg, 58%) in approximately a 2:1 ratio (from NMR). The presence of the minor diol (**36**) was evident from duplication of certain signals in the ^{1}H-NMR spectrum, viz. δ_H 1.07 (3H, s, 13β-Me) and 3.72 (1H, dd, *J* 7.8 and 3.3 Hz, 17α-H).

b) The allyl ketone (**18**) (100 mg, 0.31 mmol) was dissolved in tetrahydrofuran (7.7 cm^3) and cooled to 0°C under nitrogen. M-Borane-tetrahydrofuran (1 cm^3, 1 mmol) was added and the mixture was stirred for 90 min at 0°C, whereupon starting material was absent (TLC). 2M-Sodium hydroxide (0.5 cm^3) was slowly added to the mixture, followed by 30% hydrogen peroxide (0.25 cm^3). The suspension was allowed to stir overnight at 20°C. Water was added, and the mixture was worked-up as above (ethyl acetate) to yield a colourless oil (102 mg) which was chromatographed on silica gel (10 g). Elution with ethyl acetate-toluene (3:7) yielded the hydroxy ketone (**34**) (39 mg, 37%) as a colourless oil. This was followed by an inseparable mixture of the diols (**35**) and (**36**) (32 mg, 30%).

c) The allyl ketone (**18**) (100 mg, 0.31 mmol) in tetrahydrofuran (7.75 cm^3) was added to a stirred 0.05M solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (3.1 cm^3, 1.55 mmol) under nitrogen at 20°C. After stirring the mixture for 1 h, starting material had disappeared (TLC). Most of the tetrahydrofuran was removed under reduced pressure, and the resultant mixture was cooled to 0°C. Ethanolic M-Potassium hydroxide (0.46 cm^3) was added, followed by 30% hydrogen peroxide (0.16 cm^3).The suspension was stirred overnight at 20°C, then worked up as for (c). This yielded a colourless oil (191 mg), which was chromatographed on silica gel (19 g) using ethyl acetate-toluene (3:7) as eluent. The hydroxy ketone (**34**) (19 mg, 18%) eluted first, followed by diols (**35** and **36**) (57 mg, 53%).

Hydride Reduction of the 14β-*Allyl* 17-*Ketone* (**18**)

The allyl ketone (**18**) (190 mg, 0.58 mmol) was dissolved in tetrahydrofuran (12 cm^3) and the solution was cooled to 0°C. Lithium aluminium hydride (67 mg, 1.74 mmol) was added in small portions. The mixture was allowed to warm to 20°C with stirring. After 30 min, saturated ammonium chloride was added, and the mixture was filtered through a Celite pad, which was thoroughly washed with chloroform. The filtrate was separated and the aqueous layer was extracted twice more with chloroform. The combined organic phase was washed with saturated sodium hydrogen carbonate and brine, then dried

($MgSO_4$). Removal of the solvent under reduced pressure gave an oil (219 mg) which was chromatographed on silica gel (21 g) using ethyl acetate-toluene (1:12) as eluent. This yielded 14-*allyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* (**37**) (103 mg, 54%), m.p. 78-81°C (from chloroform-methanol); $[\alpha]_D$ +37° (*c* 1.2); ν_{max} 3609 (OH) cm^{-1}; δ_H (200 MHz) 1.09 (3H,s, 13β-Me), 2.46-2.6 (1H, m, 9α-H), 2.73-2.82 (2H, m, 6-H_2), 3.73 obsc (1H, dd, *J* 8.1 and 3.2 Hz, 17α-H), 3.76 (3H, s, 3-OMe), 4.97-5.08 (2H, m, 14^3-H), 5.9 (1H, dddd, *J* 16.8, 10, 8.7 and 5.9 Hz, 14^2-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 326.226. $C_{22}H_{30}O_2$ requires M, 326.225).

Second to elute was 14-*allyl*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**38**) (88 mg, 47%) as a colourless foam, ν_{max} 3609 (OH) cm^{-1}; δ_H (200 MHz) 1.06 (3H,s, 13β-Me), 1.44 (1H, s, exch. by D_2O, 17α-OH), 2.54 (1H, br td, *J* 2 x 11 and 3.2 Hz, 9α-H), 2.72-2.83 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.22 (1H, dd, *J* 8.8 and 7.6 Hz, 17β-H), 4.95-5.08 (2H, m, 14^3-H_2), 5.9 (1H, m, *W* 41.45 Hz, 14^2-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.7 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.4 Hz, 1-H) (Found: M^+, 326.224. $C_{22}H_{30}O_2$ requires M, 326.225).

Acetylation of the 14β-*Allyl* 17-*Alcohols* (**37**) *and* (**38**)

a) Treatment of the alcohol (**37**) (20 mg, 0.06 mmol) in pyridine (1 cm^3) with acetic anhydride (0.05 cm^3) and a catalytic amount of dimethylaminopyridine for 1 h gave, after chromatography, the derived 17β-*acetate* (**39**) as a non-crystalline product (15 mg, 67%), ν_{max} 1717 (OAc) cm^{-1}; δ_H (400 MHz) 1.02 (3H, s, 13β-Me), 1.96 (1H, dt, *J* 13 and 2 x 10.2 Hz), 2.07 (3H, s, 17β-OAc), 2,23 (1H, dq, *J* 12.4 and 3 x 3.4 Hz, 11α-H), 2.54 (1H, td, *J* 2 x 11.6 and 3.4 Hz, 9α-H), 2.69 (1H, ddt, *J* 15.3, 6.1 and 2 x 1.4 Hz), 2.77-2.81 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.82 (1H, dd, *J* 8.1 and 3.2 Hz, 17α-H), 4.97-5.08 (2H, m, 14^3-H_2), 5.95 (1H, m, *W* 42 Hz, 14^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.2 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 368. $C_{24}H_{32}O_3$ requires M, 368).

b) Similar treatment of the alcohol (**38**) (88 mg, 0.27 mmol) in pyridine (2 cm^3) with acetic anhydride (0.13 cm^3) and a catalytic amount of dimethylaminopyridine for 1 h gave, after chromatography, the derived 17α-*acetate* (**40**) as a non-crystalline product, ν_{max} 1722 (OAc) cm^{-1}; δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 2.05 (3H, s, 17α-OAc), 2.44-2.62 (1H, m, 9α-H), 2.74-2.84 (2H, m, 6-H_2), 3.67 (3H, s, 3-OMe), 4.95-5.12 (2H, m, 14^3-H_2), 5.18 obsc (1H, dd, *J* 9.1 and 6.9 Hz, 17β-H), 5.92 (2H, m, *W* 41.5 Hz,

14^2-H), 6.62 (1H, d, *J* 2.3 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.3 Hz, 2-H) and 7.24 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 368.236. $C_{24}H_{32}O_3$ requires M, 368.235).

Ketalisation of the Allyl Ketone (**18**)

Ethylene glycol (20 cm^3) and toluene-*p*-sulfonic acid (20 mg, 0.11 mmol) were added to a stirred solution of the allyl ketone (**18**) (100 mg, 0.31 mmol) in toluene (70 cm^3) under nitrogen. The mixture was refluxed in a Dean Starke apparatus, with toluene being distilled off at the rate of 35 cm^3 in 8 h. Thereafter, further ethylene glycol (20 cm^3) and toluene (20 cm^3) were added, and the reflux-distillation was continued for a futher 10 h. The mixture was extracted with toluene, and the extract was washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate, and evaporated to dryness, to give a colourless oil (125 mg) which was chromatographed on silica gel (13 g). Elution with ethyl acetate-toluene (1:24) yielded 14-allyl-17,17-ethylenedioxy-3-methoxy-14β-estra-1,3,5(10)-triene (**41**) (20 mg, 17%) as a colourless oil, δ_H (200 MHz) 0.97 (3H, s, 13β-Me), 2.72-2.8 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 3.73-3.96 (4H, m, -OCH_2CH_2O-), 4.85-5.08 (2H, m, 14^3-H_2), 5.91 (1H, m, *W* 41.9 Hz, 14^2-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.22 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 368.237. $C_{24}H_{32}O_2$ requires M, 368.235). This was followed by mixed fractions (31 mg), and then by starting material (38 mg).

3-*Methoxy*-14-*formylethyl*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**42**)

a) Oxalyl chloride (0.3 cm^3, 3 mmol) in dichloromethane (7 cm^3) was cooled to -78°C with stirring under nitrogen. Dimethyl sulfoxide (0.5 cm^3, 6 mmol) in dichloromethane (1.4 cm^3) was added and the mixture was stirred for 2 min. Diol (**35**) (68 mg, 0.2 mmol) in dichloromethane (12 cm^3) was added over 5 min, and the mixture was stirred at -78°C for 15 min. Triethylamine (1.7 cm^3, 12 mmol) was then added. After 5 min at -78°C, the mixture was allowed to warm to room temperature. Water was added and a non-crystalline residue (86 mg) was isolated by extraction into dichloromethane. Flash chromatography on silica gel (9 g) using ethyl acetate-toluene (3:17) as eluent gave the *formylethyl ketone* (**42**) (43 mg, 67%) as a colourless oil, ν_{max} 1726 (CO) cm^{-1}; δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 2.82-2.9 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.2 (1H, d, *J* 8.6 Hz, 1-H) and 9.74 (1H, t, *J* 2 x 1.2 Hz, 14^3-H) (Found: M^+, 340.203. $C_{22}H_{28}O_3$ requires M, 340.204).

b) The allyl ketone (**18**) (1.2 g, 3.7 mmol) was subjected to hydroboration-oxidation with borane-dimethyl sulfide as described previously to give a crystalline residue (1.22 g). This was dissolved in tetrahydrofuran (60 ml) and subjected to Swern oxidation conditions as described above. The recovered oil (1.24 g) was flash chromatographed on silica gel (124 g) using ethyl acetate-toluene (3:17) as eluent, yielding the formylethyl ketone (**42**) (668 mg, 53%) as a colourless oil.

c) Pyridinium chlorochromate (1.95 mmol) adsorbed on alumina (Merck Act. I, 1.95 g) was added to a stirred solution of the diols (**35** and **36**) (83 mg, 0.24 mmol) in benzene (2.5 cm^3) at 20°C under nitrogen. The mixture was stirred for 3.5 h, after which starting material was absent (TLC). The slurry was filtered through alumina and Celite pads, which were then rinsed repeatedly with chloroform. The solvent was removed under reduced pressure to yield an orange oil (55 mg) which was flash chromatographed on silica gel (6 g). Elution with ethyl acetate-toluene (3:17) gave the formylethyl ketone (**42**) (27 mg, 33%).

Attempted Retro-Aldol Approaches to the 14β-*Formylethyl* 17-*Ketones*

a) Methanolic M-potassium hydroxide (7 cm^3, 7 mmol) was added to a stirred solution of the cycloadduct (**2**) (200 mg, 0.53 mmol) in tetrahydrofuran (7 cm^3) at 20°C under nitrogen. After 2 min, water was added, followed by dilute acetic acid, and the mixture was extracted with chloroform. The organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give an oil (217 mg) which was chromatographed on silica gel (22 g) using ethyl acetate-toluene (1:9) as eluent. This yielded 3-*methoxy*-14-*formylethyl*-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**43**) (38 mg, 19%) as a colourless oil, ν_{max} 1720 and 1700 (CO) cm^{-1}; δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 2.78-2.85 (2H, m, 6-H_2), 3.74 (3H, s, 3-OMe), 6.22 (1H, d, *J* 6 Hz, 16-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.75 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.13 (1H, d, *J* 8.6 Hz, 1-H), 7.31 (1H, d, *J* 6 Hz, 15-H) and 9.74 (1H, t, *J* 2 x 1 Hz, 14^3-H) (Found: M^+, 338.188. $C_{22}H_{26}O_3$ requires M, 338.188). This was followed by an inseparable mixture of uncharacterised products (58 mg).

b) The cycloadduct (**2**) (100 mg, 0.26 mmol) was added to methanolic sodium methoxide (1.3 mmol) [prepared by reacting sodium metal (30 mg) with dry methanol (2.6 cm^3) at 40°C], and the mixture was stirred at 40-50°C for 2 h. Small portions of dry ice were added, followed by water and 2M-hydrochloric acid until the mixture was acidic. A similar work-up (chloroform) to that described in (a) gave a colourless foam (98 mg),

which was chromatographed on silica gel (10 g). Elution with ethyl acetate-toluene (1:3) yielded 3,6'β-*dimethoxy*-6'H,15αH-*dihydropyrano*[3',2':14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**44**) (43 mg, 40%), m.p. 82-85°C (from acetone-methanol); $[\alpha]_D$ +95° (*c* 0.6); ν_{max} 1723 (CO) cm^{-1}; δ_H (200 MHz) 1.1 (3H, s, 13β-Me), 2.72-2.82 (2H, m, 6-H_2), 3.35 (3H, s, 6'-OMe), 3.77 (3H, s, 3-OMe), 4.19 (1H, ddd, *J* 10.4, 6.5 and 3.5 Hz, 15α-H), 4.36 (1H, d, *J* 5.4 Hz, 6'-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.17 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 74.35; H, 8.2%; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2%; M, 370).

c) Methanolic M-potassium hydroxide (0.8 cm^3, 0.8 mmol) was added to a stirred solution of the dihydro compound (**5**) (100 mg, 0.26 mmol) in tetrahydrofuran (3.5 cm^3) under nitrogen, and the mixture stirred at 20°C for 1.5 h. The temperature was then raised to 60°C for a further 1.5 h. Water was added, followed by aqueous 3M-hydrochloric acid. Work-up (chloroform) as above, gave a semi-crystalline residue (111 mg), which was chromatographed on silica gel (11 g) using ethyl acetate-toluene (1:9) as eluent. This yielded the formylethyl ketone (**42**) (17 mg, 19%), followed by (16^{1}R)-16^1-*hydroxy*-3-*methoxy*-14,16β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**45**) (7 mg, 8%), m.p. 166-170°C; ν_{max} 3599 (OH) and 1719 (CO) cm^{-1}; δ_H (200 MHz) 1.09 (3H, s, 13β-Me), 2.64 (1H, br td, *J* 2 x 11.3 and 2.7 Hz, 9α-H), 2.72 obsc (1H, t, *J* 2 x 5.3 Hz, 16α-H), 2.82-2.9 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.09 (1H, dt, *J* 5.3 and 2 x 2.7 Hz, 16^1-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 336.187. $C_{22}H_{26}O_3$ requires M, 336.188). Further elution gave mixed fractions (24 mg), followed by (16^{1}S)-16^1-*hydroxy*-3-*methoxy*-14,16β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**46**) (23 mg, 26%), m.p. 175-180°C (from chloroform-methanol); ν_{max} 3554 (OH) and 1719 (CO) cm^{-1}; δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 1.91 (1H, s, exch. by D_2O, 16^1-OH), 2.51-2.64 (1H, m, 9α-H), 2.64 obsc (1H, dd, *J* 6.3 and 3.7 Hz, 16α-H), 2.85 (2H, m, 6-H_2), 3.77 (3H, d, *J* 0.88 Hz, 3-OMe), 3.82 (1H, ddd, *J* 10.7, 6.3 and 3.9 Hz, 16^1-H), 6.63 (1H, d, *J* 2.3 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.3 Hz, 2-H) and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 336.189. $C_{22}H_{26}O_3$ requires M, 336.188).

d) Methanolic M-potassium hydroxide (2.82 cm^3, 2.82 mmol) was added to a solution of the dimethyl ketal (**4**) (240 mg, 0.56 mmol) in tetrahydrofuran (10 cm^3) at 25°C under nitrogen. After 4 h, water was added and the mixture was acidified with M-hydrochloric acid. Work-up with chloroform as described above, yielded pale yellow crystalline material (209 mg), which was chromatographed on silica gel (21 g) using ethyl acetate-toluene (1:9) to give 3-*methoxy*-16α-(16^1,16^1-*dimethoxymethyl*)-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*ol* (**47**) (177 mg, 80%), m.p. 117-120°C (from chloroform-methanol);

$[\alpha]_D$ +139° (*c* 1.2); ν_{max} 3521 (OH) cm^{-1}; δ_H (200 MHz) 0.9 (3H, s, 13β-Me), 2.42 obsc (1H, td, *J* 8.9 and 2 x 3.9 Hz, 16β-H), 2.75-2.84 (1H, m, 9α-H), 3.25 and 3.36 (each 3H, s, 16^1-OMe_2), 3.71 (3H, s, 3-OMe), 4.18 (1H, d, *J* 8.9 Hz, 16^1-H), 5.8 and 6.0 (each 1H, d, *J* 6 Hz, 17^1- and 17^2-H), 6.56 (1H, d, *J* 2.8 Hz, 4-H), 6.65 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.16 (1H, d, *J* 8.7 Hz, 1-H) (Found: C, 74.8; H, 8.2%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 74.97; H, 8.39%; M, 384)

e) Lithium aluminium hydride (45 mg, 1.17 mmol) was added to a solution of the dimethyl ketal (**4**) (100 mg, 0.23 mmol) in tetrahydrofuran (8 cm^3) at 0°C under nitrogen. After 1 h, saturated ammonium chloride was added and the mixture was worked up (ethyl acetate) to yield a solid residue (93 mg). Chromatography on silica gel (5 g) using ethyl acetate-toluene (1:9) as eluent gave the hydroxy dimethyl ketal (**47**) (87 mg, 98%).

Intramolecular Reductive Coupling of Formylethyl Ketone (**42**)

Titanium(III)chloride-dimethoxyethane complex [formed by refluxing titanium(III) chloride in 1,2-dimethoxyethane (DME) for 2 days, then filtered under N_2 and washed with clean, dry pentane] (4.57 g, 13.7 mmol) and zinc-copper couple (2.66 g, 41 mmol) were refluxed with vigorous stirring in freshly distilled DME (100 cm^3) for 1.5 h. The black suspension was cooled to 0°C, and the formylethyl ketone (**42**) (310 mg, 0.91 mmol) in DME (150 cm^3) was added over 10 min. The mixture was allowed to warm to 20°C, the reaction being complete after 4 h (TLC). Aqueous 20% potassium carbonate (100 cm^3) was added, and the mixture was stirred overnight. Excess DME was evaporated under reduced pressure, and the slurry was extracted with ethyl acetate. The organic phase was washed (2% HCl, water, brine), dried ($MgSO_4$), and concentrated, to yield crystalline material (295 mg). Recrystallisation from ethyl acetate gave (17^1R)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^1-*diol* (**48**) (146 mg, 50%), m.p. 177-181°C; $[\alpha]_D$ +18° (*c* 1.0, THF); ν_{max} 3600 and 3450br (OH) cm^{-1}; δ_H (200 MHz) 0.88 (3H, s, 13β-Me), 2.31 (1H, br dq, *J* 12.6 and 3 x 3.3 Hz, 11α-H), 2.6 (1H, br td, *J* 2 x 10.8 and 3.1 Hz, 9α-H), 2.75-2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.99 (1H, t, *J* 2 x 8 Hz, 17^1-H), 6.61 (1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.23 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 342.217. $C_{22}H_{30}O_3$ requires M, 342.2195).

Chromatography of the mother liquor residue on silica gel (16 g) using ethyl acetate-toluene (3:7) yielded, in order of elution, starting material (**42**) (23 mg, 7%), and (17^1S)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^1-*diol* (**49**) (14 mg, 4%), m.p. 184-187°C (from ethyl acetate); $[\alpha]_D$ +21° (*c* 1.0, THF); ν_{max} 3600 and

3460br (OH) cm^{-1}; δ_H (200 MHz) 1.13 (3H, s, 13β-Me), 2.53-2.67 (1H, br td, 9α-H), 2.77-2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.84 obsc (1H, d, *J* 6.2 Hz, 17^1-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.23 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 342.217. $C_{22}H_{30}O_3$ requires M, 342.2195). This was followed by further diol (**48**) (10 mg, 3%).

Acetylation of the 17α,17^1-*Diols* (**48**) *and* (**49**)

a) Treatment of the diol (**48**) with acetic anhydride in pyridine gave (17^1R)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^1-*diol* 17^1-*acetate* (**50**), m.p. 175-178°C (from chloroform-methanol); $[\alpha]_D$ +27° (*c* 1.0); ν_{max} 3591 (OH) and 1709 (CO) cm^{-1}; δ_H (200 MHz) 0.94 (3H, s, 13β-Me), 2.09 (3H, s, 17^1-OAc), 2.3 (1H, dq, *J* 12.9 and 3 x 3.6 Hz, 11α-H), 2.59 (1H, td, *J* 2 x 11.2 and 4.5 Hz, 9α-H), 2.76-2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.32 (1H, ddd, *J* 9.8, 6.8 and 1.8 Hz, 17^1-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.23 (1H, d, *J* 8.7 Hz, 1-H); δ_C (50 MHz) 172.0 (s, 17^1-O*C*OMe), 157.5 (s, C-3), 137.8 (s, C-5), 133.3 (s, C-10), 126.4 (d, C-1), 113.5 (d, C-4), 111.5 (d, C-2), 83.2 (s, C-17), 75.4 (d, C-17^1), 55.2 (q, 3-OMe), 46.2 (s, C-13), 46.1 (s, C-14), 41.6 (d, C-8), 37.4 (d, C-9), 30.5 (t, C-6), 30.5 (t, C-16), 29.4 (t, C-12), 28.0 (t, C-17^2), 25.7 (t, C-17^3), 25.6 (t, C-15), 25.2 (t, C-11), 23.7 (t, C-7), 21.4 (q, 17^1-OCO*C*H_3) and 13.0 (q, C-18) (Found: C, 74.8; H, 8.3%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; M, 384).

b) Similar treatment of the diol (**49**) gave the corresponding (17^1S)-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17^1-*diol* 17^1-*acetate* (**51**), m.p. 181-184°C (from chloroform-methanol); $[\alpha]_D$ +36° (*c* 1.0); ν_{max} 3585 (OH) and 1727 (CO) cm^{-1}; δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 2.09 (3H, s, 17^1-OAc), 2.28 (1H, br dq, *J* 13.3 and 3 x 3.4 Hz, 11α-H), 2.62 (1H, br td, *J* 2 x 10.7 and 3.8 Hz, 9α-H), 2.78-2.86 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.9 (1H, d, *J* 5.5 Hz, 17^1-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.24 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 171.7 (s, 17^1-O*C*OMe), 157.4 (s, C-3), 137.8 (s, C-5), 133.4 (s, C-10), 126.3 (d, C-1), 113.5 (d, C-4), 111.5 (d, C-2), 82.7 (s, C-17), 78.2 (d, C-17^1), 55.2 (q, 3-OMe), 46.7 (s, C-13), 45.2 (s, C-14), 41.2 (d, C-8), 37.3 (d, C-9), 33.4 (t, C-16), 30.5 (t, C-6), 29.5 (t, C-12), 27.8 (t, C-17^3), 25.1 (t, C-15), 24.8 (t, C-11), 24.0 (t, C-17^2), 23.7 (t, C-7), 21.5 (q, 17^1-OCO*C*H_3) and 14.5 (q, C-18) (Found: C, 75.2; H, 8.2%; M^+, 384. $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; M, 384).

17α-*Hydroxy*-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17^1-*one* (**52**)

The diol (**48**) (100 mg, 0.3 mmol) in tetrahydrofuran (7 cm^3) was subjected to Swern oxidation conditions as described previously with oxalyl chloride (0.3 cm^3, 3 mmol) in tetrahydrofuran (7 cm^3), dimethyl sulfoxide (0.5 cm^3, 6 mmol) in tetrahydrofuran (1.4 cm^3), and triethylamine (1.7 cm^3, 12 mmol). This yielded semicrystalline material (360 mg), chromatography of which on silica gel (15 g) using ethyl acetate-toluene (3:17) gave the *hydroxy ketone* (**52**) (62 mg, 63%), m.p. 153-156°C (from chloroform-methanol); $[\alpha]_D$ +6° (*c* 1.0); ν_{max} 3480 (OH) and 1706 (CO) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 0.74 (3H, s, 13β-Me), 1.8 (1H, qd, *J* 3 x 10.3 and 4.1 Hz), 2.26 (1H, tdd, *J* 2 x 13.3, 4.5 and 2.5 Hz), 2.36 (1H, dq, *J* 13.4 and 3 x 3.8 Hz, 11α-H), 2.48 (1H, ddd, *J* 17.1, 7.7 and 1.4 Hz, 17^2-H_{proS}), 2.56 (1H, m, *W* 38 Hz, 17^2-H_{proR}), 2.65 (1H, td, *J* 2 x 11 and 4.1 Hz, 9α-H), 2.82-2.88 (2H, m, 6-H_2), 3.69 (1H, s, 17α-OH, exch. by D_2O), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.23 (1H, d, *J* 8.5 Hz, 1-H); δ_H (C_6D_6, 400 MHz) 0.59 (3H, s, 13β-Me), 1.17 (1H, qd, *J* 3 x 12.8 and 4.1 Hz), 2.07 obsc (1H, dq, *J* 13.4 and 3 x 3.7 Hz, 11α-H), 2.14 (1H, ddd, *J* 17.1, 7.4 and 0.7 Hz, 17^2-H_{proR}), 2.27 (1H, td, *J* 2 x 11 and 3.9 Hz, 9α-H), 2.61-2.66 (2H, m, 6-H_2), 3.44 (3H, s, 3-OMe), 3.93 (1H, s, 17α-OH, exch. by D_2O), 6.71 (1H, d, *J* 2.7 Hz, 4-H), 6.81 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.13 (1H, d, *J* 8.6 Hz, 1-H); δ_C ($CDCl_3$, 100 MHz) 214.2 (s, C-17^1), 157.6 (s, C-3), 137.7 (s, C-5), 132.7 (s, 10), 126.6 (d, C-1), 113.5 (d, C-4), 111.7 (d, C-2), 88.0 (s, C-17), 55.2 (q, 3-OMe), 47.7 (s, C-13), 46.8 (s, C-14), 42.4 (d, C-8), 37.7 (d, C-9), 32.9 (t, C-17^2), 32.6 (t, C-16), 31.6 (t, C-17^3), 30.5 (t, C-6), 29.2 (t, C-12), 25.8 (t, C-15), 25.8 (t, C-11), 23.6 (t, C-7) and 14.8 (q, C-18) (Found: C,77.4; H, 8.4%; M$^+$, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; M, 340).

Reduction of the Hydroxy Ketone (**52**)

Lithium aluminium hydride (63 mg, 1.66 mmol) was added to a stirred solution of the hydroxy ketone (**52**) (113 mg, 0.33 mmol) in tetrahydrofuran (8 cm^3) at 0°C. The mixture was allowed to warm to room temperature (*ca* 20°C). After 30 min, further lithium aluminium hydride (20 mg, 0.53 mmol) was added, and the mixture was stirred for 15 min. Saturated aqueous ammonium chloride was added, and the suspension was extracted with ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate, and evaporated under reduced pressure, to yield the (17^1*S*)-17α,17^1-diol (**49**) (100 mg, 88%).

Formation of the 3, 17α,17^1-Triols (**53**) *and* (**54**)

a) Standard demethylation (diisobutylaluminium hydride, toluene, reflux, 24 h) of the diol (**48**) (135 mg, 0.4 mmol), followed by filtration through alumina (Merck Act. III, 3 g) using ethyl acetate as eluent, gave a solid residue (128 mg), which was recrystallised from ethyl acetate to yield (17^{1}R)-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-3,17α,17^1-*triol* (**53**) (56 mg, 43%), m.p. 269-270°C (Found: C, 76.6; H, 8.8%; M$^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; M, 328).

b) Similar treatment of the diol (**49**) (32 mg, 0.094 mmol), gave (17^{1}S)-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-3,17β,17^1-*triol* (**54**) (15 mg, 47%), m.p. 251-254°C (from ethyl acetate) (Found: C, 77.0; H, 8.5%; M$^+$, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; M, 328). Insolubility in common solvents precluded full characterisation.

Similar treatment of the acetoxy alcohol (**51**) (45 mg, 0.12 mmol) gave the triol (**54**) in comparable yield (18 mg, 48%).

(17^{1}R)-3-*Methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17α,17^1-*diol* 17^1-*toluene*-p-*sulfonate* (**55**)

Toluene-*p*-sulfonyl (tosyl) chloride (167 mg, 0.88 mmol) was added to a suspension of the diol (**48**) (100 mg, 0.3 mmol) in pyridine (5 cm^3) at 0°C under nitrogen, and the mixture was kept at 7°C for 54 h. Further tosyl chloride (167 mg) was added, and the mixture left at 7°C for a further 87 h. Water was added, and the mixture was acidified with aqueous 3M-hydrochloric acid, and extracted with ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated under reduced pressure to yield a solid residue (136 mg). Chromatography on silica gel (14 g) using ethyl acetate-toluene (1:4) gave the *hydroxy tosylate* (**55**) (97 mg, 65%), m.p. 117-118°C (from chloroform-methanol); $[\alpha]_D$ +17° (*c* 1.0); ν_{max} 3585 (OH), and 1355 and 1172 (SO_2O) cm^{-1}; δ_H (200 MHz) 0.87 (3H, s, 13β-Me), 2.29 (1H, dq, *J* 13.2 and 3 x 3.9 Hz, 11α-H), 2.45 (3H, s, Ar-CH_3), 2.5-2.66 (1H, m, 9α-H), 2.77-2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.88 (1H, ddd, *J* 9.8, 7.1 and 1.5 Hz, 17^1-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), 7.2 (1H, d, *J* 8.7 Hz, 1-H), 7.34 (2H, d, *J* 8.2 Hz, 3'- and 5'-H) and 7.82 (2H, d, *J* 8.2 Hz, 2'- and 6'-H) (Found: C, 70.3; H, 7.1%; M$^+$-TsOH, 324. $C_{29}H_{36}O_5S$ requires C, 70.1; H, 7.3%; M, 496. M-TsOH, 324).

Base-Mediated Elimination of the Hydroxy Tosylate (**55**)

a) Basic alumina (Merck, Act. I, 800 mg) was added to a stirred solution of the hydroxy tosylate (**55**) (61 mg, 0.12 mmol) in dichloromethane (5.5 cm^3) at 20°C under nitrogen. After 3 h, starting material was absent (TLC). The slurry was filtered and the solvent was removed under reduced pressure to yield 3-*methoxy*-14,17α-*ethano*-17a-*homo*-14β-*estra*-1,3,5(10)-*trien*-17a-*one* (**56**) (39 mg, 98%), m.p. 161-164°C (from chloroform-methanol); $[\alpha]_D$ +32° (*c* 1.1); ν_{max} 1705 (CO) cm^{-1}; δ_H (400 MHz) 0.98 (3H, s, 13β-Me), 2.54 (1H, dddd, *J* 18.5, 14.1, 9.9 and 1.2 Hz, 17β-H), 2.86-2.92 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C 215.6 (s, C-17a), 157.5 (s, C-3), 137.5 (s, C-5), 133.6 (s, C-10), 126.6 (d, C-1), 113.8 (d, C-4), 111.6 (d, C-2), 60.7 (d, C-17), 55.2 (q, 3-OMe), 49.2 (s, C-13), 46.6 (s, C-14), 42.4 (d, C-8), 36.8 (d, C-9), 34.0 (t, C-15), 32.5 (t, C-17^2), 30.8 (t, C-6), 29.2 (t, C-12), 27.9 (t, C-16), 26.9 (t, C-17^1), 26.3 (t, C-11), 25.6 (t, C-7) and 20.9 (q, C-18) (Found: C, 81.3; H, 8.5%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; M, 324).

b) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.05 cm^3) was added to a stirred solution of the hydroxy tosylate (**55**) (5 mg, 0.01 mmol) in toluene (1 cm^3), and the mixture was heated to reflux. After 2 h, further DBU (0.05 cm^3) was added, and refluxing was continued for another 8 h. Water was added, the mixture was extracted into ethyl acetate, and the extract was washed (saturated $NaHCO_3$) and dried ($MgSO_4$). TLC comparison of the crude product with authentic material showed mainly the ketone (**56**), with a trace amount of the olefinic alcohol (**30**) present too.

(17²S)-3-*Methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10)-*triene*-17α,17²-*diol* 17²-*toluene*-p-*sulfonate* (**57**)

Toluene-*p*-sulfonyl chloride (167 mg, 0.88 mmol) was added to a suspension of the diol (**26**) (93 mg, 0.27 mmol) in pyridine (5 cm^3) at 0°C under nitrogen, and the mixture was kept at 7°C. After 24 h, water was added, the mixture was acidified with aqueous 3M-hydrochloric acid, and the crude product (130 mg) was isolated by extraction with ethyl acetate. Flash chromatography on silica gel (13 g) using ethyl acetate-toluene (1:4) gave the *hydroxy tosylate* (**57**) (105 mg, 78%), m.p. 80-82°C (from chloroform-methanol); $[\alpha]_D$ +33° (*c* 1.0); ν_{max} 3598 (OH), and 1356 and 1172 (SO_2O) cm^{-1}; δ_H 0.93 (3H, s, 13β-Me), 2.24-2.56 (1H, m, 11α-H), 2.45 (3H, s, Ar-CH_3), 2.5-2.63 (1H, m, 9α-H), 2.74-2.83 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 4.74 (1H, tt, *J* 2 x 10.3 and 2 x 7.4 Hz, 17²-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), 7.19 (1H, d, *J* 8.7 Hz, 1-H), 7.34 (2H, d, *J* 8.2 Hz, 3'- and 5'-H) and 7.8 (2H, d, *J* 8.2 Hz, 2'- and 6'-H) (Found:

C, 69.9; H, 7.2%; M^+-TsOH, 324. $C_{29}H_{36}O_5S$ requires C, 70.1; H, 7.3%; M, 496. M-TsOH, 324).

Base-Mediated Elimination of the 17α-*Hydroxy* 17^2-*Tosylate* (**57**)

a) Basic alumina (Merck, Act. I, 30 mg) was added to a stirred solution of the hydroxy tosylate (**57**) (29 mg, 0.06 mmol) in dichloromethane (2.5 cm^3) at 20°C under nitrogen. After 2 h, the slurry was filtered and the filtrate was concentrated under reduced pressure to yield an oil (19 mg), which was chromatographed on silica gel (2 g) using ethyl acetate-toluene (3:97). This gave the allyl ketone (**18**) (15 mg, 77%), followed by the olefinic alcohol (**30**) (3 mg, 16%).

b) 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1 cm^3) was added to a stirred solution of the hydroxy tosylate (**57**) (10 mg, 0.02 mmol) in toluene (2 cm^3), and the mixture was heated to reflux. After 2 h, further DBU (0.1 cm^3) was added, and refluxing was continued for a further 8 h. Water was added, and the mixture was extracted into ethyl acetate. The extract was washed (saturated $NaHCO_3$) and evaporated to dryness. TLC comparison of the crude residue with authentic material showed mainly the allyl ketone (**18**) (*ca* 90%), but also a small amount of both of the olefinic alcohols (**30** and **31**) (*ca* 5% each).

Wacker Oxidation of 14β-*Allyl*-3-*methoxy*-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**17**)

Palladium(II) chloride (275 mg, 1.55 mmol) and copper(I) chloride (800 mg, 8.07 mmol) were mixed in dimethylformamide (75 cm^3) and water (7.5 cm^3) at 20°C under an oxygen atmosphere. After 3 h, the allyl enone (**17**) (1 g, 3.1 mmol) was added and the mixture was stirred vigorously under oxygen at 65°C. After 90 min, the mixture was poured into water and 5% ammonium hydroxide was added. The mixture was extracted with toluene, and the extract was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated, to yield a yellow oil (1.188 g). Flash chromatography on silica gel (178 g) using ethyl acetate-toluene (1:9) as eluent gave 3-methoxy-14-formylethyl-14β-estra-1,3,5(10),15-tetraen-17-one (**43**) (572 mg, 55%) as an oil. This was followed by mixed fractions (136 mg), and 14-*acetonyl*-3-*methoxy*-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* (**60**) (244 mg, 23%), m.p. 132-135°C (from ethanol); $[\alpha]_D$ +139° (*c* 1.3); ν_{max} 1725br (CO) cm^{-1}; δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 2.2 (3H, s, 14^2-Me), 2.68-2.76 (2H, m, 6-H_2), 2.74 and 3.04 (each 1H, d, *J* 18.3 Hz, 14^1-H), 3.73 (3H, s, 3-OMe), 6.22 (1H, d,

J 5.9 Hz, 15-H), 6.52 (1H, d, *J* 2.8 Hz, 4-H), 6.67 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.1 (1H, d, *J* 8.6 Hz, 1-H) and 7.39 (1H, d, *J* 5.9 Hz, 16-H) (Found: C, 78.1; H, 7.8%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; M, 338).

Base Treatment of the 14β-*Acetonyl Enone* (**60**)

a) Methanolic M-potassium hydroxide (0.9 cm^3, 0.9 mmol) was added to a solution of the acetonyl enone (**60**) (107 mg, 0.3 mmol) in tetrahydrofuran (4 cm^3), and the solution was stirred at 20°C under nitrogen for 5 min. Water was added and the mixture was acidified with aqueous 3M-hydrochloric acid. Extraction with chloroform, followed by washing (saturated $NaHCO_3$, brine), drying ($MgSO_4$), and evaporation of the solvent, yielded a non-crystalline residue (102 mg) which was flash chromatographed on silica gel (10 g). Elution with ethyl acetate-toluene (1:9) yielded 3-*methoxy*-5'-*methyl*-15αH-*furano*[3',2':14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**63**) (10 mg, 10%) as a colourless oil, ν_{max} 1732 (CO) and 1669 (C:C) cm^{-1}; δ_H (200 MHz) 1.12 (3H, s, 13β-Me), 1.8 (3H, d, *J* 1 Hz, 5'-Me), 2.09 (1H, dd, *J* 19.8 and 2.6 Hz, 16β-H), 2.46-2.6 (1H, m, 9α-H), 2.78-2.88 (2H, m, 6-H_2), 3.12 (1H, dd, *J* 19.8 and 9.1 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 4.31 (1H, d, *J* 1 Hz, 4'-H), 4.95 (1H, dd, *J* 9.1 and 2.6 Hz, 15α-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 338.188. $C_{22}H_{26}O_3$ requires M, 338.188). This was followed by a multicomponent mixture (90 mg).

b) Methanolic M-potassium hydroxide (2.43 cm^3, 2.43 mmol) was added to a stirred solution of the acetonyl enone (**60**) (274 mg, 0.81 mmol) in tetrahydrofuran (10 cm^3), and the solution was heated to reflux under nitrogen for 2 h. Water was added and the mixture was acidified with aqueous 3M-hydrochloric acid. Work-up similar to that described above (chloroform) yielded a non-crystalline residue (277 mg) which was chromatographed on silica gel (28 g). Elution with ethyl acetate-toluene (1:9) yielded 3-*methoxy*-3'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*triene*-4'(5'H),17-*dione* (**61**) (175 mg, 64%), m.p. 190-193°C (from chloroform-methanol); $[\alpha]_D$ +41° (*c* 1.1); ν_{max} 1732br (CO) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.09 (3H, s, 13β-Me), 1.82-1.92 (1H, m, 16β-H), 2.02 (1H, d, *J* 19 Hz, 5'β-H), 2.24 (1H, dd, *J* 19 and 0.9 Hz, 5'α-H), 2.26 (1H, d, *J* 19.7 Hz, 3'β-H), 2.4 (1H, dq, *J* 13.3 and 3 x 3.2 Hz, 11α-H), 2.62 (1H, ddd, *J* 19.7, 6.4 and 1.6 Hz, 3'α-H), 2.76-2.86 (3H, m, 6-H_2 and 9α-H), 3.09-3.19 (2H, m, 16α- and 15α-H), 3.78 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.75 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H) and 7.23 (1H, d, *J* 8.7 Hz, 1-H); δ_H (C_6D_6, 400 MHz) 0.85 (3H, s, 13β-Me), 0.89 (1H, ddd, *J* 23.5, 12 and 6.6 Hz, 7α-H), 1.02 (1H, m, 11β-H), 1.33 (1H, dd, *J* 19.8 and

7.3 Hz, 16β-H), 1.38 (1H, m, 7β-H), 1.59 (1H, d, *J* 19.4 Hz, 5'β-H), 1.71 (1H, d, *J* 19.3 Hz, 3'β-H), 1.76 (1H, dd, *J* 19.4 and 1.1 Hz, 5'α-H), 1.88 (1H, dq, *J* 12.6 and 3 x 3.4 Hz, 11α-H), 2.08 (1H, ddd, *J* 19.3, 8 and 1.1 Hz, 3'α-H), 2.21 (1H, m, 9α-H), 2.21 (1H, m, 15α-H), 2.42-2.48 (2H, m, 6-H_2), 2.52 (1H, dd, *J* 19.8 and 10.5 Hz, 16α-H), 3.39 (3H, s, 3-OMe), 6.59 (1H, d, *J* 2.8 Hz, 4-H), 6.81 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.03 (1H, d, *J* 8.7 Hz, 1-H); δ_C ($CDCl_3$, 100 MHz) 219.2 (s, C-17), 217.8 (s, C-4'), 157.7 (s, C-3), 137.1 (s, C-5), 130.9 (s, C-10), 127.3 (d, C-1), 113.4 (d, C-4), 112.4 (d, C-2), 55.2 (q, 3-OMe), 54.5 (s, C-13), 53.9 (s, C-14), 48.2 (t, C-5'), 46.4 (t, C-3'), 44.2 (d, C-8), 43.0 (t, C-16), 38.5 (d, C-9), 32.6 (d, C-15), 31.8 (t, C-12), 31.2 (t, C-6), 26.9 (t, C-11), 25.4 (t, C-7) and 15.6 (q, C-18) (Found: C, 77.85; H, 7.7%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; M, 338).

c) Cerium(III) chloride heptahydrate (560 mg; 1.5 mmol) was dried for 2 h at 200°C/0.5 mmHg, then placed under nitrogen while still hot, and tetrahydrofuran (5 cm^3) was introduced. The suspension was stirred overnight, then cooled to -50°C, and the acetonyl enone (**60**) (200 mg, 0.6 mmol) in tetrahydrofuran (10 cm^3) was added. To this mixture was added a solution of lithium hexamethyldisilazide [formed by the slow addition of n-butyllithium (1.6M, 3.75 cm^3, 6 mmol) to a solution of hexamethyldisilazane (1.6 cm^3, 6 mmol) in tetrahydrofuran (10 cm^3) at 0°C, followed by stirring for 20 min at 0°C], also cooled to -50°C. The mixture was stirred for 1 h at -50°C, after which starting material was absent (TLC). M-Hydrochloric acid was added, and the crude product (175 mg) was isolated by extraction into chloroform. Flash chromatography on silica gel (18 g) using ethyl acetate-toluene (1:9) yielded the furano compound (**63**) (38 mg, 19%), followed by diketone (**61**) (28 mg, 14%), and then 17α-*hydroxy*-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10),15-*tetraen*-17^2-*one* (**64**) (115 mg, 58%), m.p. 227-230°C (from chloroform-methanol); $[\alpha]_D$ +124° (*c* 1.4); ν_{max} 3600 (OH) and 1702 (CO) cm^{-1}; δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 1.73 (1H, s, exch. by D_2O, 17α-OH), 1.97-2.14 (1H, m, 11α-H), 2.19 and 2.45 (each 1H, d, *J* 18.7 Hz, 17^3-H_2), 2.54 and 2.68 (each 1H, d, *J* 17.9 Hz, 17^1-H_2), 2.79-2.87 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.82 and 5.94 (each 1H, d, *J* 6 Hz, 15- and 16-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 78.4; H, 7.8%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; M, 338).

$17^2,17^2$-*Ethylenedithio*-3-*methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10),15-*tetraen*-17α-*ol* (**66**)

a) A solution of the hydroxy ketone (**64**) (84 mg, 0.25 mmol) in dichloromethane (7 cm^3) was added to a well-stirred mixture of ethane-1,2-dithiol (0.1 cm^3, 1.2 mmol) and zinc trifluoromethanesulfonate (210 mg, 0.58 mmol) in dichloromethane (2 cm^3). The mixture was stirred at 20°C under nitrogen for 1 h. Thereafter, water was added followed by sodium hydrogen carbonate to neutralise the mixture. The mixture was extracted with dichloromethane, and the combined organic layer was washed with saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The non-crystalline residue (101 mg) was chromatographed on silica gel (10 g) using ethyl acetate-toluene (1:19) as eluent. This yielded a colourless oil (35 mg, 34%), formulated as 17,17-ethylenedithio-3-methoxy-5'-methyl-15αH-furano[3',2':14,15]-14β-estra-1,3,5(10)-triene (**65**); ν_{max} 1676 (C:C) cm^{-1}; δ_H (200 MHz) 1.19 (3H, s 13β-Me), 1.82 (3H, d, *J* 1 Hz, 5'-Me), 2.77-2.84 (2H, m, 6-H_2), 3.16 (4H, m, -SCH_2CH_2S-), 3.77 (3H, s, 3-OMe), 4.26 (1H, d, *J* 1 Hz, 4'-H), 4.7 (1H, d, *J* 7.7 Hz, 15α-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 414. $C_{24}H_{30}O_2S_2$ requires M, 414).

This was followed by the non-crystalline $17^2,17^2$-*dithioketal* (**66**) (24 mg, 23%); ν_{max} 3598 (OH) cm^{-1}; δ_H (200 MHz) 1.01 (3H, s 13β-Me), 2.18 and 2.4 (each 1H, d, *J* 14.7 Hz, 17^3-H_2), 2.49 and 2.63 (each 1H, d, *J* 13.9 Hz, 17^1-H_2), 2.77-2.86 (2H, m, 6-H_2), 3.2 and 3.29 (each 2H, m, -SCH_2CH_2S-), 3.77 (3H, s, 3-OMe), 5.89 and 5.97 (each 1H, d, *J* 6 Hz, 15- and 16-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 414.168. $C_{24}H_{30}O_2S_2$ requires M, 414.169).

b) Ethane-1,2-dithiol (1 cm^3, 12 mmol) and a solution of toluene-*p*-sulfonic acid (60 mg, 0.3 mmol) in glacial acetic acid (2 cm^3) were added successively to a stirred solution of the hydroxy ketone (**64**) (128 mg, 0.38 mmol) in acetic acid (6 cm^3). The mixture was stirred at 20°C under nitrogen for 5 h, whereupon further ethane-1,2-dithiol (1 cm^3) was added. After 22 h, the mixture was poured into water and neutralised by portionwise addition of solid sodium hydrogen carbonate. Work-up similar to that described above (chloroform) yielded a colourless oil (187 mg), which was chromatographed on silica gel (18 g) using ethyl acetate-toluene (1:9) as eluent. This yielded the furano $17^2,17^2$-dithioketal (**65**) (22 mg, 14%), followed by the hydroxy $17^2,17^2$-dithioketal (**66**) (102 mg, 65%).

3-*Methoxy*-14,17β-*propano*-14β-*estra*-1,3,5(10),15-*tetraen*-17α-*ol* (**59**)

Raney nickel (Aldrich, W2, 1 g) was washed (4x) with absolute ethanol, the ethanol was decanted, and the reagent was covered with further ethanol (2 cm^3). The dithioketal (**66**) (102 mg, 0.25 mmol) was added and the mixture was refluxed under nitrogen for 2 h. The mixture was cooled and filtered through Celite, which was thoroughly rinsed with ethanol. The filtrate was concentrated under reduced pressure to yield a semi-crystalline residue (96 mg) which was chromatographed on silica gel (10 g). Elution with ethyl acetate-toluene (1:9) gave the *alcohol* (**59**) (46 mg, 58%), m.p. 145-148°C (from chloroform-methanol); $[\alpha]_D$ +91° (*c* 0.7); ν_{max} 3594 (OH) cm^{-1}; δ_H (200 MHz) 0.97 (3H, d, *J* 0.8 Hz, 13β-Me), 2.26 (1H, dq, *J* 13 and 3 x 3.4 Hz, 11α-H), 2.36-2.5 (1H, m, 9α-H), 2.77-2.86 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.69 and 5.78 (each 1H, d, *J* 6.1 Hz, 15- and 16-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.23 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.4 (s, C-3), 138.1 (s, C-5), 135.7 (d, C-16), 133.0 (d, C-10), 132.0 (d, C-15), 126.9 (d, C-1), 113.4 (d, C-4), 111.7 (d, C-2), 86.1 (s, C-17), 55.2 (q, 3-OMe), 54.4 (s, C-13), 50.8 (s, C-14), 41.7 (d, C-8), 39.4 (d, C-9), 30.8 (t, C-12), 30.0 (t, C-6), 27.5 (t, C-17^1), 26.9 (t, C-11), 23.8 (t, C-7), 22.9 (t, C-17^3), 18.5 (t, C-17^2) and 13.7 (q, C-18) (Found: M^+, 324.2095. $C_{22}H_{28}O_2$ requires M, 324.209).

14,17β-*Propano*-14β-*estra*-1,3,5(10),15-*tetraene*-3,17α-*diol* (**67**)

Standard deprotection (diisobutylaluminium hydride, toluene, reflux, 25 h) of (**59**) was followed by conventional extraction with ethyl acetate. The combined organic layer was washed with saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated to dryness, to yield a colourless, crystalline residue (65 mg), which was flash chromatographed on silica gel (7 g) using ethyl acetate-toluene (3:17) as eluent. This gave mixed fractions (7 mg) followed by the 3,17α-*diol* (**67**) (51 mg, 76%), m.p. 255-257°C (from ethyl acetate); $[\alpha]_D$ +75° (*c* 0.5, THF); δ_H (200 MHz) 0.98 (3H, s, 13β-Me), 2.36-2.5 (1H, m, 9α-H), 2.74-2.82 (2H, m, 6-H_2), 5.69 and 5.78 (each 1H, d, *J* 6.1 Hz, 15- and 16-H), 6.56 (1H, d, *J* 2.7 Hz, 4-H), 6.64 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.18 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 81.1; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; M, 310).

4'α-Hydroxy-3-methoxy-4',5'-dihydro-3'H,15αH-cyclopenta[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**68**)

Lithium tri-*sec*-butyl borohydride (2.22 cm^3, 2.22 mmol) was added to a stirred solution of the diketone (**61**) (150 mg, 0.44 mmol) in tetrahydrofuran (15 cm^3) at -60°C under nitrogen. After 30 min, saturated aqueous ammonium chloride was added and the reaction was warmed to room temperature. Work-up with ethyl acetate yielded a yellow oil (368 mg), which was chromatographed on silica gel (35 g) using ethyl acetate-hexane (3:2) as eluent. First to elute was starting material (24 mg, 16%), followed by the inseparable isomeric *hydroxy ketones* (**68**) and (**69**) (94 mg, 62%) (7:3 ratio), evident from duplication of major signals in the ^{1}H-NMR spectrum. The non-crystalline material had ν_{max} 3603 (OH) and 1725 (CO) cm^{-1}; δ_H (200 MHz) (major isomer) 1.04 (3H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 4.49 obsc (1H, qd, *J* 3 x 8.7 and 4.7 Hz, 4'β-H); (minor isomer) 1.06 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 4.6 obsc (1H, td, *J* 2 x 8.1 and 4.4 Hz, 4'α-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H). [For full characterisation of the 4'α-isomer (**68**), see later.]

Acetylation of the 4'-*Hydroxy* 17-*Ketones* (**68**) *and* (**69**)

A mixture of the hydroxy ketones (**68** + **69**, approx. 7:3) (153 mg, 0.45 mmol) was dissolved in pyridine (6 cm^3), and treated successively with acetic anhydride (0.3 cm^3, 3.2 mmol) and dimethylaminopyridine (1.5 mg, 0.012 mmol). After 30 min at room temperature, the mixture was added to water, extracted with chloroform, and the organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield an orange oil (164 mg) which was chromatographed on silica gel (16 g). Elution with ethyl acetate-toluene (1:19) gave the 4'ξ-acetoxy-3-methoxy-4',5'-dihydro-3'H,15αH-cyclopenta[14,15]-14β-estra-1,3,5(10)-trien-17-one (**70**) as an oily mixture of epimers (*ca* 7:3 ratio). The material (92 mg, 54%) had ν_{max} 1727br (CO) cm^{-1}; δ_H (200 MHz) (major component) 1.04 (3H, s, 13β-Me), 2.05 (3H, s, 4'α-OAc), 2.69 (1H, td, *J* 2 x 10.3 and 3.3 Hz, 9α-H), 2.83-2.93 (3H, m, 6-H_2 + ?), 3.77 (3H, s, 3-OMe), 5.19 (1H, qd, *J* 3 x 8.4 and 4.5 Hz, 4'β-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 219.9 (s, C-17), 170.7 (s, -OCOMe), 157.5 (s, C-3), 137.5 (s, C-5), 131.6 (s, C-10), 127.2 (s, C-1), 113.5 (s, C-4), 112.0 (s, C-2), 74.3 (d, C-4'), 56.2 and 55.4 (each s, C-13 and C-14), 55.1

(q, 3-OMe), 44.0 (d, C-8), 41.7 (t, C-16), 40.4 (d, C-9), 39.7 (d, C-15), 39.5 and 33.1 (each t, C-3' and C-5'), 35.7 (t, C-12), 31.6 (t, C-6), 26.7 (t, C-11), 25.8 (t, C-7), 21.1 (q, 4'-OCO*Me*) and 15.6 (q, C-18) (Found: M^+, 382. $C_{24}H_{30}O_4$ requires M, 382).

The minor (4'β-OH) epimer had δ_H (200 MHz) 1.99 (3H, s, 4'β-OAc), 3.76 (3H, s, 3-OMe) and 5.33 obsc (1H, td, *J* 3 x 8.4 and 4.7 Hz, 4'α-H).

3-*Methoxy*-4'(5'H)-*methylene*-3'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**71**)

n-Butyllithium (1.6M, 0.67 cm^3, 1.05 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (375 mg, 1.05 mmol) in tetrahydrofuran (6 cm^3) at 0°C under nitrogen. After 30 min, the diketone (**61**) (70 mg, 0.21 mmol) in tetrahydrofuran (3 cm^3) was added slowly at 0°C to the canary yellow suspension. The mixture was heated to reflux for 2 h, then cooled and saturated ammonium chloride was added. The mixture was extracted with ethyl acetate and the extract was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent evaporated, yielding a dark oil (351 mg) which was chromatographed on silica gel (37 g) using toluene as eluent to give the 4'-*methylene* 17-*ketone* (**71**) (90 mg, 92%), m.p. 130-134°C (from acetone-methanol), $[\alpha]_D$ +24° (*c* 0.9); ν_{max} 1728 (CO) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.05 (3H, s, 13β-Me), 1.76 (1H, m, 12-H), 1.96 (1H, ddt, *J* 17.8, 5.7 and 2 x 1.5 Hz, 16β-H), 2.02 (1H, d, *J* 18.6 Hz, 5'β-H), 2.18 (1H, d, *J* 19.7 Hz, 3'β-H), 2.19 (1H, dd, *J* 18.6 and 1.5 Hz, 5'α-H), 2.3 (1H, dq, *J* 9.8 and 3 x 3.9 Hz, 11α-H), 2.5 (1H, ddd, *J* 19.7, 8.4 and 1.5 Hz, 3'α-H), 2.73 (1H, td, *J* 2 x 11.6 and 3.1 Hz, 9α-H), 2.78-2.83 (2H, m, 6-H_2), 2.88-2.96 (1H, m, 15α-H), 3.22 (1H, ddt, *J* 17.8, 11.3 and 2 x 3.1 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 4.81-4.84 (2H, m, 4'=CH_2), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.2 (1H, d, *J* 8.7 Hz, 1-H); δ_H (C_6D_6, 400 MHz) 0.79 (3H, s, 13β-Me), 1.58 (1H, ddt, *J* 17.8, 5.8 and 2 x 1.7 Hz, 16β-H), 1.82 (1H, dd, *J* 18.5 and 1.3 Hz, 5'α-H), 1.88 (1H, d, *J* 19.3 Hz, 3'β-H), 2.01 obsc (1H, d, *J* 18.5 Hz, 5'β-H), 2.19 (1H, ddd, *J* 19.3, 8.3 and 1.3 Hz, 3'α-H), 2.27-2.36 (2H, m, 9α-H and 15α-H), 2.49-2.55 (2H, m, 6-H_2), 2.83 (1H, ddt, *J* 17.8, 11.1 and 2 x 2.6 Hz, 16α-H), 3.4 (3H, s, 3-OMe), 4.75 (2H, m, 4'=CH_2), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.82 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.12 (1H, d, *J* 8.6 Hz, 1-H); δ_C ($CDCl_3$, 100 MHz) 220.9 (s, C-17), 159.4 (s, C-4'), 157.5 (s, C-3), 137.3 (s, C-5), 131.8 (s, C-10), 127.3 (d, C-1), 113.3 (d, C-4), 112.2 (d, C-2), 105.0 (t, 4'=CH_2), 56.5 (s, C-13), 55.2 (q, 3-OMe), 49.4 (s, C-14), 48.0 (t, C-5'), 47.3 (t, C-3'), 44.1 (d, C-8), 39.2 (t, C-16), 38.5 (d, C-9), 36.1 (t, C-12), 35.7 (d, C-15), 31.4 (t, C-6), 28.0 (t, C-11), 25.9 (t, C-7) and 18.6 (q, C-18) (Found: C, 82.1; H, 8.5%; M^+, 336. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.4%; M, 336).

4',4'-*Ethylenedithio*-3-*methoxy*-3'H,5'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**72**)

a) A solution of the diketone (**61**) (50 mg, 0.15 mmol) in dichloromethane (1 cm^3) was added to a mixture of ethane-1,2-dithiol (0.05 cm^3, 0.6 mmol) and zinc trifluoromethanesulfonate (105 mg, 0.3 mmol) in dichloromethane (1 cm^3). The mixture was stirred for 1.5 h, then quenched with water and extracted with dichloromethane. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to dryness, to give a pale yellow crystalline residue (82 mg). Flash chromatography on silica gel (8.2 g) using ethyl acetate-toluene (3:97) as eluent, gave the 4',4'-*dithioketal* (**72**) (52 mg, 85%); m.p. 160-162°C (from chloroform-methanol); $[\alpha]_D$ +138° (*c* 0.8); ν_{max} 1728 (CO) cm^{-1}; δ_H (200 MHz) 1.03 (3H, s 13β-Me), 2.86-2.94 (2H, m, 6-H_2), 3.25 (4H, m, -SCH_2CH_2S-), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 414.163. $C_{24}H_{30}S_2O_2$ requires M, 414.163).

b) Ethane-1,2-dithiol (1.5 cm^3, 18 mmol) and a solution of toluene-*p*-sulfonic acid (150 mg) in glacial acetic acid (2 cm^3) were added successively to a solution of the diketone (**61**) (270 mg, 0.8 mmol) in glacial acetic acid (6 cm^3). After 18 h, the mixture was added to water and neutralised with solid sodium hydrogen carbonate. Work-up in a similar manner to that described in (a) (chloroform) gave a semi- crystalline residue (401 mg) which was flash chromatographed on silica gel (40 g) using ethyl acetate-toluene (1:49) as eluent. This yielded the dithioketal (**72**) (290 mg, 88%).

3-*Methoxy*-4',5'-*dihydro*-3'H,4'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**73**)

Raney nickel (Aldrich, W2, 1 g) was washed (4x) with absolute ethanol, the ethanol was decanted, and the nickel was covered with further ethanol (2 cm^3). A solution of the dithioketal (**72**) (289 mg, 0.7 mmol) in ethanol (16 cm^3) was added and the mixture was refluxed under nitrogen for 2 h. The mixture was cooled and filtered through Celite, which was thoroughly rinsed with ethanol. Evaporation of the solvents under reduced pressure yielded a colourless crystalline residue (227 mg) which was flash chromatographed on silica gel (12 g). Elution with ethyl acetate-toluene (3:97) gave an inseparable mixture of the desired product and a minor contaminant which co-

crystallised, formulated as the olefinic ketone (**74**). The mixture (196 mg) was treated with palladium on carbon (90 mg) in ethyl acetate (25 cm^3) under hydrogen atmosphere for 90 min. The catalyst was filtered off and the solvent was removed under reduced pressure to yield the 17-*ketone* (**73**) (189 mg, 84%), m.p. 127-130°C (from chloroform-methanol); $[\alpha]_D$ +177° (*c* 1.1); ν_{max} 1725 (CO) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.04 (3H, s, 13β-Me), 1.76 (1H, dd, *J* 19 and 6.1 Hz, 16β-H), 2.34 (1H, dq, *J* 13.3 and 3 x 3.6 Hz, 11α-H), 2.7 (1H, td, *J* 2 x 11.2 and 3.5 Hz, 9α-H), 2.82-2.86 (3H, m, 15α-H and 6-H_2), 2.87 obsc (1H, dd, *J* 19 and 10.2 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H); δ_H (C_6D_6, 400 MHz) 1.05 (3H, s, 13β-Me), 1.54 (1H, dd, *J* 19.5 and 6.5 Hz, 16β-H), 1.98 (1H, dq, *J* 12.5 and 3 x 3.5 Hz, 11α-H), 2.27 (1H, dt, *J* 10.3 and 2 x 6.5 Hz, 15α-H), 2.34 (1H, td, *J* 2 x 11.6 and 3.2 Hz, 9α-H), 2.59 obsc (1H, dd, *J* 19.5 and 10.3 Hz, 16α-H), 2.59-2.64 (2H, m, 6-H_2), 3.43 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.7 Hz, 4-H), 6.83 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.11 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 221.7 (s, C-17), 157.5 (s, C-3), 137.7 (s, C-5), 132.0 (s, C-10), 127.3 (d, C-1), 113.5 (d, C-4), 112.1 (d, C-2), 58.1 (s, C-13), 55.4 (s, C-14), 55.2 (q, 3-OMe), 44.4 (t, C-8), 42.3 (d, C-16), 39.2 (d, C-9), 37.5 (d, C-15), 34.3 (t, C-12), 33.6 (t, C-3'), 33.0 (t, C-4'), 31.7 (t, C-6), 27.2 (t, C-11), 25.5 (t, C-7), 23.2 (t, C-5') and 15.7 (q, C-18) (Found: C, 81.6; H, 8.5%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; M, 324).

Hydride Reduction of the 17-Ketone (**73**)

Lithium aluminium hydride (75 mg, 1.99 mmol) was added to a stirred solution of the ketone (**73**) (214 mg, 0.66 mmol) in tetrahydrofuran (13 cm^3) at 0°C under nitrogen. After 40 min at 0°C, the reaction was complete (TLC) and saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate and the combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated under reduced pressure, to yield a colourless oil (228 mg) which was chromatographed on silica gel (23 g) using ethyl acetate-toluene (1:19) as eluent. First to elute was 3-*methoxy*-4',5'-*dihydro*-3'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* (**75**) (39 mg, 18%), m.p. 67-70°C (from chloroform-methanol); $[\alpha]_D$ +72° (*c* 1.2); ν_{max} 3562 (OH) cm^{-1}; δ_H (200 MHz) 1.07 (3H, s, 13β-Me), 2.15-2.29 (1H, m, 11α-H), 2.44-2.58 (2H, m, 9α- and 15α-H), 2.64 (1H, ddd, *J* 15.1, 11.1 and 7 Hz, 16α-H), 2.76-2.86 (2H, m, 6-H_2), 3.68 (1H, dd, *J* 7 and 1.1 Hz, 17α-H), 3.77 (3H, s, 3-OMe), 6.6 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.23 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.3 (s, C-3), 138.1 (s, C-5), 133.1 (s, C-10), 127.2 (d, C-1), 113.4 (d, C-4), 111.9 (d, C-2), 82.3 (d, C-17), 59.7 (s, C-13), 55.2 (q, 3-OMe), 49.4 (s, C-14), 45.1 (d,

C-8), 43.2 (d, C-9), 41.5 (t, C-16), 39.7 (d, C-15), 37.1 (t, C-12), 35.1 (t, C-3'), 33.1 (t, C-4'), 31.9 (t, C-6), 27.3 (t, C-11), 25.7 (t, C-7), 23.6 (t, C-5') and 16.7 (q, C-18) (Found: M^+, 326.225. $C_{22}H_{30}O_2$ requires M, 326.225).

Second to elute was 3-*methoxy*-4',5'-*dihydro*-3'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**76**) (145 mg, 67%), m.p. 67-70°C (from chloroform-methanol); $[\alpha]_D$ +66° (*c* 0.6); ν_{max} 3596 (OH) cm^{-1}; δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 1.3 (1H, m, 15α-H), 1.98 (1H, ddd, *J* 13.7, 11.5 and 9.5 Hz, 16β-H), 2.32 (1H, dq, *J* 12.3 and 3 x 3.5 Hz, 11α-H), 2.44-2.5 (1H, m, 15α-H), 2.5-2.58 (1H, m, 9α-H), 2.78-2.87 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 3.93 (1H, dd, *J* 9.5 and 8.9 Hz, 17β-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.26 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.4 (s, C-3), 137.9 (s, C-5), 133.0 (s, C-10), 127.1 (d, C-1), 113.4 (d, C-4), 111.8 (d, C-2), 80.6 (d, C-17), 58.6 (s, C-13), 55.2 (q, 3-OMe), 47.2 (s, C-14), 44.6 (d, C-8), 40.5 (d, C-9), 39.4 (t, C-16), 39.1 (d, C-15), 35.8 (t, C-12), 33.0 (t, C-3'), 31.6 (t, C-6), 30.2 (t, C-4'), 26.5 (t, C-11), 25.8 (t, C-7), 24.9 (t, C-5') and 19.7 (q, C-18) (Found: C, 80.9; H, 9.1%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; M, 326).

Deprotection of the 3-*Methyl Ethers* (**75**) *and* (**76**)

a) Diisobutylaluminium hydride (DIBAH) (1.5M, 2 cm^3, 3 mmol) was added to a stirred solution of the alcohol (**75**) (77 mg, 0.24 mmol) in toluene (20 cm^3). The mixture was refluxed under nitrogen for 24 h, then cooled and extracted with ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to dryness to yield a non-crystalline residue (96 mg). Chromatography on silica gel (9 g) using ethyl acetate-toluene (1:4) as eluent gave 3'H,15αH-4',5'-*dihydrocyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*triene*-3,17β-*diol* (**77**) (73 mg, 99%), m.p. 159-161°C (from chloroform); $[\alpha]_D$ +66° (*c* 0.5, THF) (Found: C, 81.0; H, 9.1%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; M, 312).

b) Similar treatment of the alcohol (**76**) (100 mg, 0.31 mmol) gave, after chromatography, 3'H,15αH-4',5'-*dihydrocyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* (**78**) (97 mg, 99%), m.p. 213-215°C (from chloroform); $[\alpha]_D$ +73° (*c* 0.6, THF) (Found: C, 80.6; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; M, 312).

Intramolecular Reductive Coupling of the Diketone (**61**)

The diketone (**61**) (236 mg, 0.7 mmol) in tetrahydrofuran (8 cm^3) was added to samarium(II) iodide (3.3 mmol) in tetrahydrofuran (85 cm^3). The mixture was refluxed for 1 h under nitrogen, then water (56 cm^3) was added. After refluxing for a further 16 h, 0.05M-hydrochloric acid was added, and the mixture was extracted into ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to dryness to yield pale yellow crystalline material (238 mg) which was flash chromatographed on silica gel (24 g) using ethyl acetate-hexane (7:3) as eluent. First to elute was starting material (9 mg, 4%), followed by an inseparable mixture (204 mg) of the hydroxy ketone (**68**) and diol (**79**) which coeluted (204 mg).

Treatment of the mixture (204 mg) with acetone (6 cm^3) and 70% aqueous perchloric acid (0.013 cm^3) for 4 h, followed by the addition of saturated sodium hydrogen carbonate, and similar work-up (chloroform) to that described above, gave a non-crystalline residue (228 mg). Chromatography on silica gel (23 g) using ethyl acetate-toluene (1:9) gave (17^{2}R)-16β,17β-*isopropylidenedioxy*-3-*methoxy*-16α,17^2-*methano*-14,17α-*ethanoestra*-1,3,5(10)-*triene* (**80**) (22 mg, 8%), m.p. 181-184°C (from chloroform-methanol); $[\alpha]_D$ +69° (*c* 0.7); δ_H (200 MHz) 1.07 (3H, s, 13β-Me), 1.54 and 1.55 (each 3H, s, CMe_2), 2.27 (1H, dq, *J* 13 and 3 x 3.4 Hz, 11α-H), 2.78-2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 157.5 (s, C-3), 138.1 (s, C-5), 132.1 (s, C-10), 127.3 (d, C-1), 119.9 (s, *C*Me_2), 113.7 (d, C-4), 111.8 (d, C-2), 93.2 and 91.9 (each s, C-16 and C-17), 55.2 (q, 3-OMe), 52.7 (s, C-13), 50.4 (t, C-17^1), 50.2 (s, C-14), 45.5 and 42.2 (each t, C-15 and C-16^1), 40.8 (d, C-8), 39.3 (d, C-9), 34.9 (t, C-17^2), 34.8 (d, C-12), 30.4 (t, C-6), 28.4 and 28.2 (each q, C*Me*$_2$), 28.0 (t, C-11), 24.1 (t, C-7) and 20.6 (q, C-18) (Found: C, 79.0; H, 8.6%; M^+, 380. $C_{25}H_{32}O_3$ requires C, 78.9; H, 8.5%; M, 380).

This was followed by starting material (**61**) (26 mg, 13%), and hydroxy ketone (**68**) (123 mg, 60%), δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 2.02 (1H, dd, *J* 15.5 and 9.8 Hz), 2.1 (1H, dd, *J* 13.3 and 7.6 Hz), 2.64-2.78 (2H, m, 9α-H and 15α-H), 2.8-2.9 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.49 (1H, dq, *J* 3 x 8.7 and 4.7 Hz, 4'-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 220.8 (s, C-17), 157.6 (s, C-3), 137.8 (s, C-5), 131.8 (s, C-10), 127.2 (s, C-1), 113.4 (s, C-4), 112.1 (s, C-2), 56.5 and 55.4 (each s, C-13 and C-14), 55.2 (q, 3-OMe), 44.1 (d, C-8), 43.3 (t, C-16), 43.0 (t, C-3'), 42.1 (t, C-5'), 39.6 (d, C-9), 36.1 (t, C-12), 33.2 (t, C-15), 31.7 (t, C-6), 26.8 (t, C-11), 26.1 (t, C-7) and 15.8 (q, C-18) (Found: M^+, 340.202. $C_{22}H_{28}O_3$ requires M, 340.204).

Reduction of the 4'-*Hydroxy* 17-*Ketone* (**68**)

Methanesulfonyl chloride (0.1 cm^3, 1.3 mmol) was added to a solution of the hydroxy ketone (**68**) (110 mg, 0.32 mmol) in pyridine (4 cm^3) at 0°C. The mixture was stirred at 0°C under nitrogen for 2 h. Water and M-hydrochloric acid were added and the mixture was extracted with ethyl acetate. The organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield a yellowish oil (163 mg) which was flash chromatographed on silica gel (16 g) using ethyl acetate-hexane (1:3) as eluent. A colourless oil, formulated as 4'α-*methanesulfonyloxy*-3-*methoxy*-3',5'-*dihydro*-4'αH,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**83**) (107 mg, 80%) (Found: M^+, 418. $C_{23}H_{30}O_5S$ requires M, 418) was isolated. The material was immediately dissolved in tetrahydrofuran (6 cm^3) and treated with lithium aluminium hydride (40 mg, 1 mmol). The mixture was heated to reflux under nitrogen for 2 h, then cooled, quenched (saturated NH_4Cl), and worked-up in a similar manner to that described above (ethyl acetate). The crude residue (97 mg) was chromatographed on silica gel (10 g) using ethyl acetate-toluene (1:19) as eluent. This yielded 17β-alcohol (**75**) (19 mg, 18%) followed by 17α-alcohol (**76**) (49 mg, 47%).

Intramolecular Reductive Coupling of the Formylethyl Enone (**42**)

Titanium(III) chloride-dimethoxyethane complex (8.0 g, 24 mmol) and zinc-copper couple (4.2 g, 65 mmol) were refluxed with vigorous stirring in freshly distilled dimethoxyethane (DME) (160 cm^3) for 1.5 h. The black suspension was cooled to 0°C, and the formylethyl enone (**43**) [contaminated with *ca* 10% of the diketone (**60**)] (360 mg, 1.07 mmol) in DME (250 cm^3) was added over 10 min. The mixture was stirred for 30 min at 0-5°C, whereupon the reaction was complete (TLC). Aqueous 20% potassium carbonate (160 cm^3) was added, and the mixture was left to stir overnight. Excess DME was evaporated off under reduced pressure, and the slurry was extracted with ethyl acetate. The organic phase was washed (2% HCl, water, brine), dried ($MgSO_4$), and concentrated under reduced pressure, to yield a colourless foam (419 mg). Chromatography on silica gel (24 g) using ethyl acetate-toluene (1:3) as eluent gave the diketone (**61**) (33 mg, 9%). This was followed by 3'α-*hydroxy*-3-*methoxy*-4',5'-*dihydro*-3'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**84**) (39 mg, 11%), m.p.

The monoacetylated derivative of the hydroxy ketone (**85**), *viz.* 3'β-*acetoxy*-3-*methoxy*-4',5'-*dihydro*-3'H,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**87**) had m.p. 103-106°C (from acetone-methanol); $[\alpha]_D$ +108° (*c* 1.1); ν_{max} 1725 (CO) cm^{-1}; δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 2.01 (1H, s, 3'-OAc), 2.27 (1H, dd, *J* 20.1 and 6.9 Hz, 16β-H), 2.59 (1H, dd, *J* 20.1 and 10 Hz, 16α-H), 2.62-2.78 (1H, m, 9α-H), 2.8-2.91 (2H, m, 6-H_2), 3.12 (1H, dt, *J* 10 and 2 x 6.9 Hz, 15α-H), 3.77 (3H, s, 3-OMe), 5.28 (1H, dt, *J* 9.3 and 2 x 6.9 Hz, 3'α-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 219.9 (s, C-17), 170.7 (s, 3'-*O*COMe), 157.6 (s, C-3), 137.4 (s, C-5), 131.5 (s, C-10), 127.3 (d, C-1), 113.4 (d, C-4), 112.2 (d, C-2), 77.1 (d, C-3'), 56.4 (s, C-13), 55.2 (q, 3-OMe), 55.1 (s, C-14), 43.9 (d, C-8), 40.2 (d, C-9), 39.0 (d, C-15), 35.4 (t, C-16), 33.3 (t, C-12), 31.5 (t, C-6), 31.2 (t, C-4'), 28.9 (t, C-5'), 26.9 (t, C-11), 25.8 (t, C-7), 21.0 (q, 3'-OCO*Me*) and 14.8 (q, C-18) (Found: C, 75.2; H, 7.9; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9%; M, 384).

3-*Methoxy*-4',5'-*dihydro*-15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-3',17-*dione* (**88**)

Oxalyl chloride (0.4 cm^3, 4 mmol) in dichloromethane (9 cm^3) was cooled to -78°C with stirring under nitrogen. Dimethyl sulfoxide (0.67 cm^3, 8 mmol) in dichloromethane (1.9 cm^3) was added and the mixture stirred for 2 min. A mixture of hydroxy ketones (**84** and **85**) (130 mg, 0.38 mmol) in a 3:7 ratio (obtained from the 'mixed fractions' described above which were isolated during chromatography of the intramolecular coupling reaction residue) in dichloromethane (11 cm^3) was added over 5 min, and the mixture was stirred at -78°C for 35 min. Triethylamine (2.3 cm^3, 16 mmol) was added, and the mixture was stirred at -78°C for 5 min, and then allowed to warm to room temperature. Water was added and the mixture extracted with dichloromethane The combined organic phase was washed with saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure to yield a solid residue (163 mg). Chromatography on silica gel (16 g) using ethyl acetate-toluene (1:9) as eluent gave the 3',17-*diketone* (**88**) (114 mg, 89%), m.p. 177-178°C (from chloroform-methanol); $[\alpha]_D$ + 154° (*c* 0.9); ν_{max} 1732br (CO) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.1 (3H, s, 13β-Me), 1.8 (1H, m, 5'α-H), 1.93 (1H, ddd, *J* 13.5, 9.6 and 3 Hz, 5'β-H), 2.05 (1H, m, 16β-H), 2.38 obsc (1H, dq, *J* 13.1 and 3 x 3.7 Hz, 11α-H), 2.41 obsc (1H, dd, *J* 20.2 and 9.6 Hz, 4'β-H), 2.52 (1H, ddd, *J* 20.2, 11.6 and 3.2 Hz, 4'α-H), 2.56-2.62 (2H, m, 9α-H), 2.84-2.89 (2H, m, 6-H_2), 2.95-3.04 (2H, m, 15α-H and 16β-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz,

1-H); δ_H (C_6D_6, 400 MHz) 0.89 (3H, s, 13β-Me), 1.72 (1H, m, 16β-H), 2.05 (1H, td, *J* 2 x 11.3 and 2.4 Hz, 9α-H), 2.5-2.6 (4H, m, 6-H_2, 15α-H and 16α-H), 3.43 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.81 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.02 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 218.4 and 217.6 (each s, C-3' and C-17), 157.7 (s, C-3), 136.9 (s, C-5), 130.8 (s, C-10), 127 (d, C-1), 113.4 (d, C-4), 112.2 (d, C-2), 55.2 (q, 3-OMe), 54.5 and 53.8 (each s, C-13 and C-14), 46.9 (d, C-15), 43.8 (d, C-8), 38.2 (d, C-9), 36.9 (t, C-16), 35.8 (t, C-4'), 33.1 (t, C-12), 30.4 (t, C-5'), 30.2 (t, C-6), 26.3 (t, C-11), 24.1 (t, C-7) and 13.8 (q, C-18) (Found: C, 78.2; H, 7.9%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; M, 338).

Mesylation of 3'-*Hydroxy* 17-*Ketones* (**84**) *and* (**85**)

Treatment of the formylethyl enone (**43**) (430 mg, 1.3 mmol) with titanium(III) chloride-dimethoxyethane complex as described above, followed by chromatography, gave a mixture of the hydroxy ketones (**84**) and (**85**) (340 mg, 80%) in a 3:7 ratio (from NMR). This mixture of epimers (**84** + **85**) (340 mg, 1 mmol) in pyridine (15 cm^3) at 0°C, was treated with methanesulfonyl chloride (0.31 cm^3, 4 mmol), and stirred under nitrogen for 30 min. Water and M-hydrochloric acid were added, and the mixture was extracted into ethyl acetate. The combined organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure. The resultant oil (385 mg) was flash chromatographed on silica gel (42 g) using ethyl acetate-toluene (1:9) as eluent. First to elute was 3'β-*methanesulfonyloxy*-3-*methoxy*-4',5'-*dihydro*-3'αH,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**89**) (202 mg, 48%), m.p. 183-187°C (from chloroform-methanol); $[\alpha]_D$ +91° (*c* 0.8); ν_{max} 1729 (CO) and 1171 (OSO_2) cm^{-1}; δ_H (200 MHz) 1.04 (3H, s, 13β-Me), 2.31 obsc (1H, dd, *J* 20.1 and 6.8 Hz, 16β-H), 2.74 (1H, dd, *J* 20.1 and 10 Hz, 16α-H), 2.86-2.93 (2H, m, 6-H_2), 3.01 (3H, s, 3'β-OMs), 3.18 (1H, dt, *J* 10 and 2 x 6.8 Hz, 15α-H), 3.7 (3H, s, 3-OMe), 5.32 (1H, ddd, *J* 14.4, 8.1 and 6.8 Hz, 3'α-H), 6.63 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 65.7; H, 7.2%; M^+, 418. $C_{23}H_{30}O_5S$ requires C, 66.0; H, 7.2%; M, 418).

This was followed by mixed fractions (30 mg, 7%), and then by 3'α-*methanesulfonyloxy*-3-*methoxy*-4',5'-*dihydro*-3'βH,15αH-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**90**) (94 mg, 22%), m.p. 141-143°C (from acetone-diisopropyl ether); $[\alpha]_D$ +164° (*c* 1.0); ν_{max} 1731 (CO) and 1172 (OSO_2) cm^{-1}; δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 2.51 (1H, td, *J* 2 x 10.2 and 3.3 Hz, 9α-H), 2.83-2.9 (2H, m, 6-H_2), 2.98 (3H, s, 3'β-OMs), 3.78 (3H, s, 3-OMe), 5.0 (1H, dd, *J* 7.7 and 2.7 Hz, 3'-H), 6.63 (1H, d,

J 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 65.9; H, 7.3%; M^+, 418. $C_{23}H_{30}O_5S$ requires C, 66.0; H, 7.2%; M, 418).

Reduction of the 3'β-*Mesyloxy* 17-*Ketones* (**89**) *and* (**90**)

a) Lithium aluminium hydride (74 mg, 1.9 mmol) was added to a tetrahydrofuran (15 cm^3) solution of the mesyloxy ketone (**89**) (202 mg, 0.48 mmol), and the mixture was refluxed for 5 h. Saturated ammonium chloride was added, and the mixture was extracted with chloroform. The combined organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure, to yield a non-crystalline residue (170 mg).

b) In a similar reaction, the epimeric mesyloxy ketone (**90**) (25 mg, 0.08 mmol) in tetrahydrofuran (4 cm^3) was refluxed with lithium aluminium hydride (30 mg, 0.8 mmol) for 2 h. The crude material after similar work-up (chloroform) to that described above (18 mg) was combined with the comparable (TLC) material obtained in the preceding experiment on (**89**) (170 mg). This material (240 mg) was chromatographed on silica gel (24 g) using ethyl acetate-toluene (1:19) as eluent. First to elute was the 17β-alcohol (**75**) (29 mg, 12%), followed by the epimeric 17α-alcohol (**76**) (126 mg, 52%). Thereafter, unidentified, polar material (44 mg) was eluted.

Attempted Hydrocyanation of Allyl Ketone (**18**)

Trimethylsilyl cyanide (0.1 cm^3) and zinc(II) iodide (15 mg) were added to a stirred solution of the allyl ketone (**18**) (200 mg, 0.62 mmol) in dichloromethane (6 cm^3), and the mixture was refluxed under nitrogen for 3 h. Water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure. The residue so isolated (288 mg) was chromatographed on silica gel (29 g) using toluene → ethyl acetate-toluene (1:9) gradient elution. First to elute was a non-crystalline product formulated as (17^2S)-17^2-iodo-3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17α-ol 17-trimethylsilyl ether (**91**), δ_H (200 MHz) 0.08 (9H, s, 17α-OTMS), 0.93 (3H, s, 13β-Me), 1.93 obsc (1H, t, 2 x 12 Hz, 17^3-H_{proS}), 2.14 (1H, dd, *J* 12 and 6.9 Hz, 17^1-H_{proS}), 2.23 obsc (1H, dd, *J* 12 and 6.9 Hz, 17^3-H_{proR}), 2.56 obsc (1H, t, *J* 2 x 12 Hz, 17^1-H_{proR}), 2.74-2.83 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 4.38 (1H, tt, *J* 2 x 12 and 2 x 6.9 Hz, 17^2-H_R), 6.6 (1H, d, *J* 2.6

Hz, 4-H), 6.71 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H) and 7.21 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 524. $C_{25}H_{37}IO_2Si$ requires M, 524).

This was followed by an inseparable mixture of epimers (1:2 from NMR) of 14β-allyl-3-methoxy-17ξ-trimethylsilyloxy-14β-estra-1,3,5(10)-triene-17ξ-carbonitrile (**92**), ν_{max} 2228 (CN) cm^{-1}; δ_H (200 MHz) (minor isomer) 0.25 (9H, s, 17ξ-OTMS), 1.28 (3H, s, 13β-Me), 5.06-5.19 (2H, m, 14^3-H_2); (major isomer) 0.29 (9H, s, 17ξ-OTMS), 1.15 (3H, s, 13β-Me), 4.93-5.06 (2H, m, 14^3-H_2); 2.74-2.84 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.79-6.03 (1H, m, 14^2-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 423. $C_{26}H_{37}NO_2Si$ requires M, 423).

Third to elute was (17^2S)-17^2-iodo-3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17α-ol (**93**), ν_{max} 3591 (OH) cm^{-1}; δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 1.96 (1H, t, 2 x 12 Hz, 17^3-H_{proS}), 2.17 (1H, dd, *J* 12 and 7 Hz, 17^1-H_{proS}), 2.27 obsc (1H, dd, *J* 12 and 7 Hz, 17^3-H_{proR}), 2.58 obsc (1H, t, *J* 2 x 12 Hz, 17^1-H_{proR}), 2.77-2.86 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.8 (1H, tt, *J* 2 x 12 and 2 x 7 Hz, 17^2-H_R), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 157.4 (s, C-3), 137.5 (s, C-5), 132.8 (s, C-10), 126.2 (d, C-1), 113.3 (d, C-4), 111.5 (d, C-2), 82.5 (s, C-17), 55.1 (q, 3-OMe), 19.9 (s, C-13), 48.6 (t, $C\text{-}17^1$), 45.2 (s, C-14), 44.8 (t, $C\text{-}17^3$), 41.1 (d, C-8), 37.3 (d, C-9), 33.2 (t, C-12), 30.3 (t, C-6), 28.7 (t, C-16), 25.5 (t, C-11), 24.2 (t, C-15), 23.6 (t, C-7), 20.4 (d, $C\text{-}17^2$) and 13.9 (q, C-18) (Found: M^+, 452. $C_{22}H_{29}IO_2$ requires M, 452).

14β-*Propyl*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**94**)

10% Palladium on carbon was added to a solution of the allyl ketone (**18**) (150 mg, 0.47 mmol) in ethyl acetate (8 cm^3), and the mixture was stirred vigorously under 1 atm hydrogen for 3.5 h. The catalyst was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue (158 mg) was chromatographed on silica gel (15 g) using ethyl acetate-toluene (1:49) as eluent. This yielded the 14β-*propyl* 17-*ketone* (**94**) (132 mg, 87 %), m.p. 114-117°C (from acetone-methanol); $[\alpha]_D$ +52° (*c* 1.0); ν_{max} 1723 (CO) cm^{-1}; δ_H (400 MHz) 0.85 (3H, t, 2 x 7 Hz, 14^2-Me), 1.04 (3H, s, 13β-Me), 2.01 (1H, m, 7-H), 2.13-2.21 (1H, m, 15-H), 2.25 (1H, dd, *J* 19 and 9.5 Hz, 16α-H), 2.30 (1H, dq, *J* 13.2 and 3 x 3.4 Hz, 11α-H), 2.43-2.53 (1H, m, 16β-H), 2.58-2.65 (1H, m, 9α-H), 2.84-2.89 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 222.9 (s, C-17), 157.6 (s, C-3), 137.9 (s, C-5), 132.6 (s, C-10), 126.5 (d, C-1), 113.6 (d, C-4), 111.7 (d, C-2), 55.2 (q, 3-OMe), 52.7 (s, C-13), 46.6 (s, C-14), 42.0 (d, C-8), 41.0 (t,

C-14[1]), 38.0 (d, C-9), 33.8 (t, C-16), 33.0 (t, C-12), 30.6 (t, C-6), 25.7 (t, C-11), 25.5 (t, C-15), 23.8 (t, C-7), 18.5 (t, C-14[2]), 15.6 (q, C-18) and 15.1 (q, C-14[3]) (Found: C, 81.0; H, 9.0%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; M, 326).

14β-*Allyl*-3-*methoxy*-14β-*estra*-1,3,5(10),16-*tetraen*-17-*yl* 17-*trimethylsilyl ether* (**95**)

A solution of the allyl ketone (**18**) (100 mg, 0.31 mmol) in tetrahydrofuran (THF) (7 cm^3) was added slowly to a stirred mixture of lithium diisopropylamide (1.75 mmol; generated by adding 0.7 cm^3 2.5M n-BuLi to a solution of 0.5 cm^3 diisopropylamine in 0.5 cm^3 THF at 0°C) at -78°C under nitrogen. After 45 min, chlorotrimethylsilane (0.6 cm^3, 3.1 mmol) was added, and the mixture was warmed to 0°C. Saturated ammonium chloride was added, and the product was extracted into chloroform. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield the silyl enol ether (**95**) as an oily residue (185 mg) which was too unstable for further purification, ν_{max} 1638 (C=C) cm^{-1}; δ_H 0.22 (9H, s, 17-OTMS), 1.01 (3H, s, 13β-Me), 2.74-2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.34 (1H, dd, *J* 2.9 and 1.7 Hz, 16-H), 4.85-5.01 (2H, m, 14[3]-H_2), 5.9 (1H, m, *W* 42 Hz, 14[2]-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+ 396. $C_{25}H_{36}O_2Si$ requires M, 396).

14-*Allyl*-3-*methoxy*-15α<u>H</u>,16α<u>H</u>-*cyclopropa*[15,16]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**96**)

Trimethylsulfoxonium iodide (250 mg, 1.13 mmol) was added in small portions to a suspension of 60% sodium hydride (45 mg, 1.13 mmol) in dimethylformamide (DMF) (1 cm^3). The mixture was stirred at room temperature under nitrogen for 30 min, after which period a solution of the allyl enone (**17**) (100 mg, 0.31 mmol) in DMF (1 cm^3) was added. The mixture was heated to 110°C for 90 min, then cooled, poured into cold M-hydrochloric acid, and extracted with ethyl acetate. The extract was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to yield a crystalline residue (116 mg). Purification of this crude product by chromatography on silica gel (12 g) using ethyl acetate-toluene (1:24), yielded the *cyclopropyl ketone* (**96**) (86 mg, 83%), m.p. 144-147°C (from chloroform-methanol); $[\alpha]_D$ +273° (*c* 1.0); ν_{max} 1705 (CO) cm^{-1}; δ_H (200 MHz) 1.04 (1H, m, 3'-H), 1.11 (3H, s, 13β-Me), 1.96 (1H, m, 3'-H), 2.76 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 5.07-5.23 (2H, m, 14[3]-H_2), 5.86 (1H, m, *W* 41.6 Hz, 14[2]-H), 6.57

(1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.04 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 81.8; H, 8.4%; M^+, 336. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.4%; M, 336).

14-*Allyl*-3-*methoxy*-15β-*methyl*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**97**)

A solution of the cyclopropyl ketone (**96**) (117 mg, 0.35 mmol) in tetrahydrofuran (10 cm^3) was added to a rapidly stirred mixture of lithium metal (30 mg, 8.8 g atom) in anhydrous liquid ammonia (15 cm^3) (freshly distilled from sodium) at -78°C. The mixture was stirred at -78°C for 10 min, then solid NH_4Cl was added slowly. The ammonia was allowed to evaporate, and the product was extracted into ethyl acetate. The organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to dryness, to yield an oily residue (153 mg) which was adsorbed onto silica gel (16 g). Elution with ethyl acetate-toluene (3:97) yielded mixed fractions of starting material and product (18 mg), followed by pure 15β-*methyl* 17-*ketone* (**97**) (78 mg, 66%), m.p. 147-149°C (from chloroform-methanol); $[\alpha]_D$ +118° (*c* 1.2); ν_{max} 1723 (CO) cm^{-1}; δ_H (200 MHz) 1.14 (3H, s, 13β-Me), 1.22 (3H, d, *J* 6.5 Hz, 15β-Me), 2.57 (1H, dd, *J* 14.9 and 7.8 Hz, 16β-H), 2.73 obsc (1H, dd, *J* 14.9 and 9.3 Hz, 16α-H), 2.82 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.03-5.19 (2H, m, 14^3-H_2), 5.75 (1H, m, *W* 40.9 Hz, 14^2-H), 6.62 (1H, d, *J* 2.5 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H) and 7.22 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 81.6; H, 9.0%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; M, 338).

14-*Propyl*-3-*methoxy*-15α<u>H</u>,16α<u>H</u>-*cyclopropa*[15,16]-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**98**)

10% Palladium on carbon (50 mg) was added to a solution of the cyclopropyl ketone (**96**) (143 mg, 0.43 mmol) in ethanol (7 cm^3), and the mixture was stirred under 1 atm hydrogen pressure for 6h. The catalyst was filtered off through celite, and the solvent was removed under reduced pressure, to yield a crystalline residue (148 mg), which was chromatographed on silica gel (15 g). Elution with ethyl acetate-toluene (1:19) gave the 14β-*propyl* 17-*ketone* (**98**) (124 mg, 85%), m.p. 135-136°C (from acetone-methanol); $[\alpha]_D$ +239° (*c* 1.3); ν_{max} 1705 (CO) cm^{-1}; δ_H (200 MHz) 0.96 (3H, t, *J* 2 x 6.8 Hz, 14^3-Me), 1.0 (1H, m, 3'-H), 1.03 (3H, s, 13β-Me), 1.93 (1H, m, 3'-H), 2.24 (1H, m, 9α-H), 2.78 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.58 (1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.04 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 219.3 (s, C-17), 157.0 (s, C-3), 137.2 (s, C-5), 134.8 (s, C-10), 128.8 (d, C-1), 112.9 (d, C-4), 112.5 (d, C-2), 55.2 (q, 3-OMe), 49.6 (s, C-14), 46.0 (s, C-13), 39.6 (d, C-8), 36.3 (d, $C-14^1$), 32.4

(d, C-9), 31.8 (t, C-12), 30.9 (t, C-6), 29.2 (t, C-11), 28.4 (d, C-16), 26.6 (d, C-15), 25.1 (q, 14^3-Me), 23.3 (t, C-7), 17.9 (t, C-14^2), 14.8 (q, C-18) and 11.3 (t, C-3') (Found: C, 81.3; H, 8.9%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; M, 338).

14-*Allyl*-15β,16β-*epoxy*-3-*methoxy*-14β-*estra*-1,3,5(10)-*trien*-17-*one* (**99**)

Aqueous 4M-sodium hydroxide (0.1 cm^3, 0.4 mmol) was added to a stirred solution of the allyl enone (**17**) (100 mg, 0.31 mmol) in methanol (10 cm^3), and the mixture was cooled to 0 °C. 30% Hydrogen peroxide (1 cm^3) was added dropwise, and the mixture was allowed to warm to room temperature (24°C). After 3 h, saturated sodium sulfite and saturated ammonium chloride were added, and the product was isolated by extraction into chloroform. The organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and the solvent was removed under reduced pressure, to yield a semi-crystalline residue (99 mg). This crude product was purified on silica gel (10 g) using ethyl acetate-toluene (1:19) as eluent, to yield the *epoxy ketone* (**99**) (84 mg, 81%), m.p. 114-116°C (from acetone-methanol); $[\alpha]_D$ +270° (*c* 1.0); ν_{max} 1737 (CO) cm^{-1}; δ_H (200 MHz) 1.21 (3H, s, 13β-Me), 2.74 (2H, m, 6-H_2), 3.48 (1H, d, *J* 2.4 Hz, 15α-H), 3.73 (1H, d, *J* 2.4 Hz, 16α-H), 3.76 (3H, s, 3-OMe), 5.13-5.27 (2H, m, 14^3-H_2), 5.88 (1H, dddt, *J* 16.7, 9.9, 8.3 and 6.2 Hz, 14^2-H), 6.57 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.03 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 77.7; H, 7.8%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; M, 338).

14-*Allyl*-15β,16β-*epoxy*-3-*methoxy*-17β-*methyl*-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* (**100**)

1.5 M Methyllithium (37 cm^3, 55.5 mmol) was added dropwise to a solution of the epoxy ketone (**99**) (625 mg, 18.5 mmol) in tetrahydrofuran (20 cm^3) at -78°C under nitrogen. After 45 min, saturated ammonium chloride was added, and the product was extracted into chloroform. The organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield a colourless oil (740 mg). Chromatography of this residue on silica gel (74 g) using ethyl acetate-toluene (1:19) as eluent, gave the *epoxy alcohol* (**100**) (704 mg, 93%) as a colourless foam, $[\alpha]_D$ +131° (*c* 0.6); ν_{max} 3607 (OH) cm^{-1}; δ_H (400 MHz) 0.93 (3H, s, 13β-Me), 1.19-1.29 (1H, m, 11β-H), 1.41 (3H, s, 17β-Me), 1.77-1.86 (1H, m, 12-H), 2.1-2.16 (1H, m, 7-H), 2.32-2.41 (1H, m, 11α-H), 2.48-2.55 (2H, m, 14^1-H_2), 2.69-2.78 (2H, m, 6-H_2), 3.35 (1H, d, *J* 2.6 Hz, 15α-H), 3.46 (1H, d, *J* 2.6 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 5.0-5.12 (2H, m, 14^3-H_2), 5.85 (1H, m, *W* 41.4 Hz, 14^2-H), 6.6 (1H, d, *J* 2.5 Hz, 4-H), 6.71 (1H, dd, *J* 8.5

and 2.5 Hz, 2-H) and 7.18 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 157.3 (s, C-3), 137.9 (s, C-5), 136.2 (d, C-14^2), 133.5 (s, C-10), 117.0 (t, C-14^3), 113.2 (d, C-4), 112.0 (d, C-2), 81.0 (s, C-17), 65.1 (d, C-15), 63.1 (d, C-16), 55.2 (q, 3-OMe), 53.9 (s, C-13), 49.4 (s, C-14), 41.1 (d, C-8), 37.7 (t, C-14^1), 37.5 (d, C-9), 33.2 (t, C-12), 30.8 (t, C-6), 29.6 (t, C-11), 24.3 (t, C-7), 24.0 (q, 17-Me) and 20.4 (q, C-18) (Found: M$^+$, 354. $C_{23}H_{30}O_3$ requires M, 354).

14-*Allyl*-15β,16β-*epoxy*-3-*methoxy*-17β-*methyl*-14β-*estra*-1,3,5(10)-*trien*-17-*yl acetate* (**101**)

Acetic anhydride (0.1 cm^3, 1.4 mmol) and dimethylaminopyridine (*ca.* 5 mg) were added to a stirred solution of the epoxy alcohol (**100**) (50 mg, 0.14 mmol) in pyridine (2 cm^3) at 20°C. After 26h, further acetic anhydride (0.1 cm^3) was added, and the mixture was allowed to stir for a further 46h. Water was added, followed by 3M-hydrochloric acid, and the products were isolated by extraction into ethyl acetate. Chromatography of the residue (86 mg) on silica gel (9 g) using ethyl acetate-hexane (3:17) as eluent, gave the *epoxy acetate* (**101**) (10 mg, 18%), $[\alpha]_D$ +49° (*c* 0.8); ν_{max} 1724 (OAc) cm^{-1}; δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 1.56 (3H, s, 17β-Me), 2.09 (3H, s, 17α-OAc), 2.76 (2H, m, 6-H$_2$), 3.46 (1H, d, *J* 2.6 Hz, 15α-H), 3.77 (3H, s, 3-OMe), 4.04 (1H, d, *J* 2.6 Hz, 16α-H), 5.0-5.14 (2H, m, 14^3-H$_2$), 5.86 (1H, m, *W* 41.5 Hz, 14^2-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.16 (1H, d, *J* 8.5 Hz, 1-H) (Found: M$^+$, 396. $C_{25}H_{32}O_4$ requires M, 396).

This was followed by mixed fractions (28 mg).

14-*Allyl*-15β,16β-*epoxy*-3-*methoxy*-17β-*methyl*-14β-*estra*-1,3,5(10)-*trien*-17α-yl 17-*trimethylsilyl ether* (**102**)

Bistrimethylsilylacetamide (BSA) (0.1 cm^3, 0.4 mmol) was added to a solution of the epoxy alcohol (**100**) (50 mg, 0.14 mmol) in dimethylformamide (2 cm^3) under nitrogen, and the mixture was heated to 80°C. After 6h, further BSA (0.1 cm^3) was added. After a total time of 75 h, water and 3M-hydrochloric acid were added, and the mixture was extracted with ethyl acetate. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield an oily residue (79 mg), which was adsorbed on to silica gel (8 g). Elution with ethyl acetate-hexane (1:9) gave the *epoxide* (**102**) (26 mg, 44%) as a non-crystalline product, $[\alpha]_D$ +73° (*c* 1.2); δ_H (200 MHz) 0.23 (9H, s, 17α-OTMS), 0.92 (3H, s, 13β-Me), 1.41 (3H, s, 17β-Me), 2.74 (2H,

m, 6-H_2), 3.32 (1H, d, *J* 2.6 Hz, 15α-H), 3.44 (1H, d, *J* 2.6 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 5.0-5.14 (2H, m, 14^3-H_2), 5.87 (1H, m, *W* 41.2 Hz, 14^2-H), 6.6 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.16 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 426. $C_{26}H_{38}O_3Si$ requires M, 426).

This was followed by mixed fractions (11 mg), and then by starting material (12 mg, 24%).

14-*Allyl*-3-*methoxy*-17β-*methyl*-14β-*estra*-1,3,5(10),15-*tetraen*-17α-*ol* (**103**)

1.5 M Methyllithium (4 cm^3, 6.4 mmol) was added dropwise to a solution of the allyl enone (**17**) (220 mg, 0.64 mmol) in tetrahydrofuran (4 cm^3) at -78°C under nitrogen. After 1 h, saturated ammonium chloride was added, and the product was extracted into chloroform. The organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield a non-crystalline residue (237 mg). Chromatography of this material on silica gel (24 g) using ethyl acetate-toluene (1:19) as eluent, gave the *methyl alcohol* (**103**) (187 mg, 85%) as a colourless oil, $[\alpha]_D$ +70° (*c* 1.0); ν_{max} 3609 (OH) cm^{-1}; δ_H (200 MHz) 1.14 (3H, s, 13β-Me), 1.45 (3H, s, 17β-Me), 1.69 (1H, s, 17α-OH, exch. by D_2O), 2.77 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.97-5.08 (2H, m, 14^3-H_2), 5.62 (1H, d, *J* 5.9 Hz, 16-H), 5.83 (1H, d, *J* 5.9 Hz, 15-H), 5.87 (1H, m, *W* 41.4 Hz, 14^2-H), 6.61 (1H, d, *J* 2.5 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H) and 7.23 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 338. $C_{23}H_{30}O_2$ requires M, 338).

Reduction of the 15β,16β-*Epoxy* 17α-*Alcohol* (**100**)

Lithium aluminium hydride (87 mg, 2.1 mmol) was added to a stirred solution of epoxy alcohol (**100**) (250 mg, 0.7 mmol) in tetrahydrofuran (15 cm^3) at 0°C. The mixture was refluxed under nitrogen for 2h, then cooled, and saturated ammonium chloride was added slowly. The mixture was extracted with ethyl acetate, and the combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated, to give a non-crystalline residue (265 mg). The material was dissolved in pyridine (5 cm^3) and treated with acetic anhydride (0.2 cm^3, 2.1 mmol) and dimethylaminopyridine (*ca* 5 mg) at 0°C. After 45 min, water was added, followed by 3M-hydrochloric acid. The mixture was worked up in a similar manner to that described above, to yield an oily residue (323 mg). Chromatography of this material on silica gel (33 g) using ethyl acetate-toluene (1:9 → 1:5) yielded four products. First to elute was a non-crystalline compound, diacetate (**104**) (98 mg, 32%), ν_{max} 1731 (OAc) cm^{-1}; δ_H (400 MHz) 0.78 (3H, d, *J* 7.2 Hz, Me), 1.04

(3H, s, 13β-Me), 1.09-1.2 (1H, m, 7-H), 1.21-1.32 (1H, m, 11β-H), 1.37 (1H, dt, *J* 14.1 and 2 x 3.3 Hz, 12-H), 1.57 (1H, td, *J* 2 x 11.5 and 1.2 Hz, 8β-H), 1.53 (1H, td, *J* 2 x 14.1 and 3.5 Hz, 12-H), 1.94-2.01 (1H, m, 7-H), 2.05 and 2.07 (each 3H, s, 2 x OAc), 2.34 (1H, dq, *J* 12.7 and 3 x 3.2 Hz, 11α-H), 2.45-2.54 (2H, m, ? and 14^1-H), 2.6 (1H, dd, *J* 15.3 and 9 Hz, 14^1-H), 2.7-2.78 (3H, m, 9α-H and 6-H_2), 3.76 (3H, s, 3-OMe), 5.03-5.15 (2H, m, 14^3-H_2), 5.26 (1H, dd, *J* 9.8 and 5 Hz), 5.73 (1H, d, *J* 5 Hz), 5.97 (1H, m, *W* 41.4 Hz, 14^2-H), 6.58 (1H, d, *J* 2.8 Hz, 4-H), 6.7 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 170.8 and 170.2 (each s, 2 x *O*COMe), 157.5 (s, C-3), 137.7 (s, C-5), 136.6 (d, C-14^2), 132.7 (s, C-10), 127.1 (d, C-1), 117.2 (t, C-14^3), 113.4 (d, C-4), 111.8 (d, C-2), 79.8 and 79.7 (each d), 55.2 (q, 3-OMe), 51.0 (s, C-13), 45.4 (s, C-14), 42.9 (d), 41.3 (d, C-8), 38.0 (d, C-9), 33.8 (t, C-14^1), 31.8 (t, C-12), 31.3 (t, C-6), 27.0 (t, C-11), 24.0 (t, C-7), 21.4 and 21.0 (each q, 2 x OCO*Me*), 20.5 (q, C-18) and 7.2 (q, 17-Me) (Found: M^+, 440. $C_{27}H_{36}O_5$ requires M, 440).

Second to elute was another non-crystalline diacetate (**105**) (76 mg, 25%), ν_{max} 1736 (OAc) cm^{-1}; δ_H (400 MHz) 0.98 (3H, d, *J* 7.2 Hz, Me), 1.07 (3H, s, 13β-Me), 1.12-1.22 (1H, m, 7-H), 1.26 (1H, qd, *J* 3 x 12.4 and 4.6 Hz, 11β-H), 1.39 (1H, m, 12-H), 1.61 (1H, td, *J* 2 x 11.5 and 1.4 Hz, 8β-H), 1.92-1.99 (1H, m, 7-H), 2.01 and 2.06 (each 3H, s, 2 x OAc), 2.24 (1H, t, *J* 2 x 6.4 Hz), 2.28 (1H, dq, *J* 13.3 and 3 x 3.5 Hz, 11α-H), 2.48 (1H, br dd, *J* 15.8 and 5.5 Hz, 14^1-H), 2.64-2.75 (4H, m, 14^1-H, 9α-H and 6-H_2), 3.75 (3H, s, 3-OMe), 5.0 (1H, dd, *J* 8.2 and 6.4 Hz), 5.01-5.14 (2H, m, 14^3-H_2), 5.62 (1H, d, *J* 8.2 Hz), 5.96 (1H, m, *W* 41.2 Hz, 14^2-H), 6.57 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.2 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 170.3 and 169.5 (each s, 2 x *O*COMe), 157.5 (s, C-3), 137.8 (s, C-5), 136.8 (d, C-14^2), 132.7 (s, C-10), 127.0 (d, C-1), 117.0 (t, C-14^3), 113.5 (d, C-4), 111.7 (d, C-2), 76.7 (d), 71.1 (d), 55.2 (q, 3-OMe), 51.1 (s, C-13), 47.8 (d), 42.9 (s, C-14), 40.8 (d, C-8), 37.7 (d, C-9), 33.3 (t, C-14^1), 32.3 (t, C-12), 31.1 (t, C-6), 26.9 (t, C-11), 23.9 (t, C-7), 20.9 and 20.9 (each q, 2 x OCO*Me*), 20.8 (q, C-18) and 11.5 (q, 17-Me) (Found: M^+, 440. $C_{27}H_{36}O_5$ requires M, 440).

Third to elute was an unidentified crystalline compound (**106**) (15 mg, 5%), ν_{max} 1727 (OAc) cm^{-1}; δ_H (200 MHz) 0.87 (3H, s, Me) 1.09 (3H, s, 13β-Me), 2.08 (3H, s, OAc), 2.68 (1H, br td, 9α-H), 2.78-2.87 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.2 (1H, t, *J* 2 x 3.2 Hz), 4.25 (1H, s), 5.0 (1H, s), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.25 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 396. $C_{25}H_{32}O_2$ requires M, 396).

The last of the four compounds was non-crystalline and had the structure of a hydroxy acetate (**107**) (56 mg, 20%), ν_{max} 3602 (OH) and 1724 (OAc) cm^{-1}; δ_H (400 MHz) 1.07 (3H, s, 13β-Me), 1.13-1.23 (1H, m, 7-H), 1.24-1.36 (1H, m, 11β-H), 1.5 (3H, s, Me), 1.51 obsc (1H, dt, *J* 14.1 and 2 x 3.2 Hz, 12-H), 1.6-1.68 (1H, m, 8β-H), 1.81

(1H, dd, *J* 14.7 and 9 Hz), 1.91 (1H, td, *J* 2 x 14.1 and 3.8 Hz, 12-H), 2.02 (3H, s, OAc), 2.3-2.41 (2H, m, 11α-H and 14^1-H), 2.44 (1H, dd, *J* 14.7 and 9 Hz), 2.68-2.78 (3H, m, 9α-H and 6-H_2), 2.89 (1H, dd, *J* 15.9 and 8.3 Hz, 14^1-H), 3.76 (3H, s, 3-OMe), 5.02-5.14 (2H, m, 14^3-H_2), 5.65 (1H, t, *J* 2 x 9 Hz), 5.92 (1H, m, *W* 41.4 Hz, 14^2-H), 6.57 (1H, d, *J* 2.7 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 170.4 (s, O*C*OMe), 157.5 (s, C-3), 137.8 (s, C-5), 136.3 (d, C-14^2), 132.7 (s, C-10), 127.3 (d, C-1), 116.9 (t, C-14^3), 113.5 (d, C-4), 111.8 (d, C-2), 79.2 (s), 72.7 (d), 55.2 (q, 3-OMe), 51.6 (s, C-13), 49.6 (s, C-14), 45.9 (d), 41.0 (d, C-8), 37.8 (d, C-9), 33.6 (t, C-14^1), 33.4 (t, C-12), 31.3 (t, C-6), 30.8 (q, Me), 28.0 (t, C-11), 23.9 (t, C-7), 21.4 (q, OCO*Me*) and 18.0 (q, C-18) (Found: M^+, 398. $C_{25}H_{34}O_2$ requires M, 398).

Silyl Enol Ether Formation – Cyclopropanation of Estrone 3-Methyl Ether (**108**)

Estrone 3-methyl ether (**108**) (1.68 g, 5.9 mmol) in tetrahydrofuran (120 cm^3) was added to a stirred solution of lithium diisopropylamide (33 mmol; 22 cm^3 1.5M n-butyllithium and 10 cm^3 diisopropylamine in 10 cm^3 tetrahydrofuran at 0°C) at -78°C under nitrogen. After 45 min, chlorotrimethylsilane (10 cm^3, 78 mmol) was added, and the mixture was warmed to 0°C. After 45 min, saturated ammonium chloride was added, and the mixture was extracted with chloroform. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated to yield the silyl enol ether (**109**) (2.76 g) as pale yellow crystalline material. This was dissolved in benzene (80 cm^3), and M-diethyl zinc (7 cm^3, 7 mmol) and diiodomethane (1.2 cm^3, 14.9 mmol) were added sequentially. The mixture was stirred at 20°C for 30 min, then water was added and the product was extracted into ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated to dryness, to yield a solid residue (4.4 g) which was flash chromatographed on silica gel (260 g) using toluene as eluent. This gave 3-*methoxy*-16β<u>H</u>-*cyclopropa*-[16,17]-*estra*-1,3,5(10)-*triene*-17β-*ol* 17-*trimethylsilyloxy ether* (**110**) (1.87 g, 86%), m.p. 116-118°C (from acetone-methanol); $[\alpha]_D$ +78° (*c* 0.6); δ_H (200 MHz) 0.15 (9H, s, 17β-OTMS), 0.74 (1H, dd, *J* 9 and 6.3 Hz, 3'-H_{exo}), 0.87 (1H, m, 16β-H), 0.99 (3H, s, 13β-Me), 1.01 (1H, dd, *J* 6.3 and 4 Hz, 3'-H_{endo}), 2.15 (1H, m, 9α-H), 2.84 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.19 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 157.4 (s, C-3), 137.9 (s, C-5), 132.8 (s, C-10), 126.1 (d, C-1), 113.8 (d, C-4), 111.4 (d, C-2), 70 (s, C-17), 55.2 (q, 3-OMe), 46.7 (d, C-14), 44.6 (d, C-9), 43.4 (s, C-13), 37.7 (d, C-8), 33.6 (t, C-12), 29.7 (t, C-6), 27.4 (t, C-7), 26.4 (t, C-11), 25.9 (d, C-16), 21.4 (t, C-15), 15.4 (t, C-3'), 13.6 (q, C-18), 1.4 (q, 17-OTMS) (Found: C, 74.5; H, 9.3%; M^+, 370. $C_{23}H_{34}O_2Si$ requires C, 74.5; H, 9.3%; M, 370).

3-*Methoxy*-17a-*homoestra*-1,3,5(10),16-*tetraen*-17a-*one* (**111**)

A solution of the trimethylsilyloxy cyclopropyl compound (**110**) (1.87 g, 5.1 mmol) and pyridine (0.41 cm^3, 5.1 mmol) in dimethylformamide (80 cm^3) was added dropwise over 2h to a solution of anhydrous iron(III) chloride (2.57 g, 15.2 mmol) in dimethylformamide (40 cm^3) at 0°C under nitrogen. The mixture was warmed to 20°C and stirred for 30 min, then poured into cold M-hydrochloric acid (130 cm^3). Work-up into chloroform yielded a crystalline residue (1.7 g), to which was added methanol (100 cm^3) and sodium acetate (2 g, 24 mmol). This mixture was refluxed under nitrogen overnight, then cooled. Water was added and the mixture was extracted with chloroform. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated to dryness under reduced pressure to yield pale yellow crystalline material (1.5 g), which was chromatographed on silica gel (100 g) using ethyl actetate-toluene (1:19) as eluent. This gave the 17a-*homo enone* (**111**) (1.32 g, 88%), m.p. 150-153 °C (from acetone-methanol); $[\alpha]_D$ -0.6° (*c* 1.0); ν_{max} 1665 cm^{-1} (CO); λ_{max} 231 nm (lit.[107] λ_{max} 255 nm); δ_H (400 MHz) 1.04 (s, 3H, 13β-Me), 1.36 (1H, m, 7β-H), 1.78 (1H, dt, *J* 10.9 and 2 x 4.5 Hz, 14α-H), 2.04 (1H, m, 15α-H), 2.12 (1H, dt, *J* 13.8 and 2 x 3.2 Hz, 12-H), 2.26 (1H, td, *J* 2 x 10.9 and 3.8 Hz, 9α-H), 2.38 (1H, dq, *J* 13.3 and 3 x 3.6 Hz, 11α-H), 2.56 (1H, dt, *J* 19.2 and 2 x 4.5 Hz, 15β-H), 2.86 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.95 (1H, ddd, *J* 10.1, 3 and 1.1 Hz, 17-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.8 Hz, 2-H), 6.89 (1H, ddd, *J* 10.1, 6 and 2.1 Hz, 16-H) and 7.22 (1H, d, *J* 8.8 Hz, 1-H); δ_C (100) 205.5 (s, C-17a), 157.6 (s, C-3), 147.5 (d, C-16), 137.5 (s, C-5), 132.2 (s, C-10), 127.8 (d, C-17), 126.4 (d, C-1), 113.5 (d, C-4), 111.7 (d, C-2), 55.2 (q, 3-OMe), 45.5 (d, C-14), 44.6 (s, C-13), 42.6 (d, C-9), 39.3 (d, C-8), 32.3 (t, C-12), 30 (t, C-6), 27.2 (t, C-15), 25.9 (t, C-7), 25.9 (t, C-11) and 15.7 (q, C-18) (Found: C, 80.6; H, 8.16%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.16%; M, 296).

3-*Methoxy*-17β-*trimethylsilyloxyestra*-1,3,5(10)-*triene*-17α-*carbonitrile* (**112**)

Trimethylsilyl cyanide (0.050 cm^3, 0.37 mmol) and zinc(II) iodide (5 mg, 15.6 μmol) were added successively to a solution of estrone 3-methyl ether (**108**) (100 mg, 0.35 mmol) in dichloromethane (3 cm^3) at 20°C under nitrogen. The mixture was refluxed for 3 h, and then cooled. Water was added, and the mixture extracted with dichloromethane. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure. The residue (134 mg) was chromatographed on silica

gel (13 g) using ethyl acetate-toluene (1:99) as eluent, to yield the *carbonitrile* (**112**) (112 mg, 84%), m.p. 138-141°C (from acetone-methanol); $[\alpha]_D$ +10° (*c* 0.9); ν_{max} 2227 (CN) cm^{-1}; δ_H (200 MHz) 0.24 (9H, s, 17β-OTMS), 0.83 (3H, s, 13β-Me), 2.26 (1H, m, 9α-H), 2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 72.1; H, 8.4%; M^+, 382. $C_{23}H_{32}NO_2Si$ requires C, 72.2; H, 8.4%; M, 382).

3-*Methoxy*-17α-*methyl-estra*-1,3,5(10)-*trien*-17β-*ol* (**114**)

Estrone 3-methyl ether (**108**) (100 mg, 0.35 mmol) in ether (6 cm^3) and tetrahydrofuran (4 cm^3) was added to a stirred suspension of methylmagnesium iodide (80 mg Mg and 0.2 cm^3 methyl iodide in 4 cm^3 ether) at 20°C under nitrogen. After 2.5 h, saturated ammonium chloride was added, and the product was extracted into ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure, to yield a pale yellow crystalline residue (103 mg). This was chromatographed on silica gel (10 g) using ethyl acetate-toluene (1:19) as eluent, to give the methyl alcohol (**114**) (76 mg, 72%), m.p. 89-92°C (from acetone-isopropyl ether); $[\alpha]_D$ +47°C (*c* 1.0); ν_{max} 3602 (OH) cm^{-1}; δ_H (200 MHz) 0.89 (3H, s, 13β-Me), 1.27 (3H, s, 17α-Me), 1.59 (1H, s, 17β-OH, exch. by D_2O), 2.84 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 79.7; H, 9.6%; M^+, 300. $C_{20}H_{28}O_2$ requires C, 79.9; H, 9.4%; M, 300).

Dehydration of the 17α-*Methyl* 17β-*Alcohol* (**114**)

a) Toluene-*p*-sulfonic acid (104 mg, 0.55 mmol) was added to a solution of the methyl alcohol (**114**) (33 mg, 0.11 mmol) in benzene (3 cm^3). The mixture was refluxed under nitrogen for 90 min, then cooled. Water was added, and the products were extracted into ethyl acetate to yield a crystalline residue (33 mg), which was adsorbed on to silica gel (4 g). Elution with ethyl acetate-hexane (1:49) gave an inseparable mixture of compounds (1:4 ratio from NMR) (20 mg, 65%). The major component of the mixture was formulated as 3-methoxy-17,17-dimethyl-14β-estra-1,3,5(10),13-tetraene (**115**), m.p. 115-119°C (from acetone-methanol); δ_H 1.02 (6H, s, 17-Me_2), 2.62-2.73 (2H, m, 9α-H and 6-H_2), 3.78 (3H, s, 3-OMe), 6.67 (1H, d, *J* 2.7 Hz, 4-H), 6.7 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.11 (1H, d, *J* 8.6 Hz, 1-H); δ_C 157.7 (s, C-3), 137.0 (s, C-5), 135.6 (s, C-10), 129.7 (s, C-13), 125.3 (d, C-1), 122.7 (s, C-14), 113.4 (d, C-4), 110.8 (d, C-2),

55.2 (q, 3-OMe), 48.2 (d, C-8), 42.7 (d, C-9), 42.0 (s, C-17), 37.3 (t, C-12), 30.3 (t, C-6), 30.0 (t, C-16), 29.0 (q, 17-Me), 27.9 (t, C-15), 25.6 (q, 17-Me), 24.7 (t, C-11) and 22.5 (t, C-7) (Found: M^+, 282. $C_{20}H_{26}O$ requires M, 282).

b) Methyl triphenoxyphosphonium iodide (330 mg, 0.73 mmol) was added to a solution of the methyl alcohol (**114**) (100 mg, 0.33 mmol), in hexamethylphosphoric triamide (1.5 cm^3), and the mixture was heated to 100°C for 24 h, then to 150°C for a further 48 h. The mixture was cooled, poured into 2M-potassium hydroxide (10 cm^3), and extracted with ethyl acetate. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was removed under reduced pressure, to yield an oily residue (235 mg). Chromatography on silica gel (24 g) using ethyl acetate-hexane (1:49) as eluent gave a crystalline mixture of the 17-methylene and Δ^{16}-17-methyl isomers (**116**) and (**117**) (2:5 ratio from NMR) (76 mg, 82%). The exocyclic methylene compound (**116**) had δ_H (200 MHz) 0.83 (3H, s, 13b-Me), 2.85 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.31 (2H, ddd, *J* 3.1 and 2 x 1.5 Hz, 20-H_2), 6.67 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H) and 7.2 (1H, d, *J* 8.7 Hz, 1-H). The endocyclic methylene compound (**117**) had δ_H (200 MHz) 0.76 (3H, s, 13β-Me), 1.67 (1H, d, *J* 2 Hz, 17-Me), 2.85 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.68 (1H, t, *J* 2.2 Hz, 16-H), 6.67 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H) and 7.2 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 282. $C_{20}H_{26}O$ requires M, 282).

c) Phosphorous oxychloride (0.1 cm^3, 1 mmol) was added to a solution of the methyl alcohol (**114**) (100 mg, 0.33 mmol) in pyridine (3 cm^3). The mixture was stirred at 20°C under nitrogen for 16 h, then poured into ice-water and acidified with cold 3M-hydrochloric acid. Extraction of the products into ethyl acetate, followed by washing (saturated $NaHCO_3$, brine), drying ($MgSO_4$), and evaporation of the solvents, yielded an oily residue (83 mg). This was chromatographed on silica gel (8.5 g) using toluene as eluent, to give a mixture of (**116**) and (**117**) (65 mg, 70%) in a 1:2 ratio (from NMR).

3-*Methoxy*-17β-*methyl-estra*-1,3,5(10)-*triene*-16α,17α-*diol* (**120**)

16α-Hydroxy-3-methoxy-1,3,5(10)-estratrien-17-one (**118**) (100 mg, 0.33 mmol) in ether (6 cm^3) and tetrahydrofuran (4 cm^3) was added to a suspension of methyl magnesium iodide (80 mg Mg and 0.2 cm^3 methyl iodide in 4 cm^3 ether) and the mixture was stirred at 20°C for 1 h. Saturated ammonium chloride was added, and the mixture was extracted with chloroform. The organic layer was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and the solvent was removed under reduced pressure, to yield a crystalline

residue (112 mg). Chromatography on silica gel (11 g) using ethyl acetate-toluene (1:4) as eluent gave starting material (15 mg), followed by an inseparable mixture (3:2 from NMR) (67 mg, 64%). The major component of the mixture was isolated by recrystallisation of the mixed fractions from ethyl acetate and rechromatography of this material. This major product was identified as the diol (**120**), m.p. 152-154°C (from methanol); $[\alpha]_D$ +30.6° (*c* 1.1) (lit.[139] m.p. 155°; $[\alpha]_D$ +30.5°); ν_{max} 3523 and 3490sh (OH) cm^{-1}; δ_H (200 MHz) 0.73 (3H, s, 17β-Me), 1.21 (3H, s, 13β-Me), 2.22 (1H, s, -OH, exch. by D_2O), 2.84 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 4.11 (1H, dd after exch. by D_2O, *J* 9.1 and 2.6 Hz, 16β-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H,dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 316. $C_{20}H_{28}O_3$ requires M, 316).

The minor component was formulated as the isomeric 3-methoxy-16ξ-methyl-estra-1,3,5(10)-triene-16ξ,17β-diol (**121**), ascertained from duplication of certain signals in the NMR spectrum of the mixture *viz.* 0.74 (3H, s, 13β-Me), 1.22 (3H, s, 16ξ-Me), 3.88 (1H, d, *J* 5.3 Hz, 17α-H).

Oxidative Cleavage - Intramolecular Aldol Condensation of the 17-*Methyl*-16,17-*Diol and* 16-*Methyl* 16,17-*Diol Mixture*

A chromatographically clean mixture (3:2 from NMR) of the diols (**120** + **121**) (2 g, 6.67 mmol) was dissolved in benzene (165 cm^3) and the solution was treated with lead(IV) acetate (5.52 g, 12.5 mmol). After 10 min at 20°C, water and 3M-hydrochloric acid were added, and the products were isolated by extraction with ethyl acetate. The brown oily residue obtained (1.94 g) was flash chromatographed on silica gel (194 g) using ethyl acetate-toluene (3:97) as eluent, to give 3-methoxy-16-methyl-16,17-secoestra-1,3,5(10)-trien-16,17-dione (**122**) (20 mg, 1%), ν_{max} 1716 (CO) cm^{-1}; δ_H (200 MHz) 1.03 (3H, s, 13β-Me), 2.17 (3H, s, 16-Me), 2.82 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.3 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.3 Hz, 2-H), 7.2 (1H, d, *J* 8.6 Hz, 1-H) and 9.37 (1H, s, 17-H); δ_C (50 MHz) 206.7 and 206.1 (each s, C-16 and C-17), 157.7 (s, C-3), 137.5 (s, C-5), 131.5 (s, C-10), 126.4 (d, C-1), 113.5 (d, C-4), 111.9 (d, C-2), 55.2 (q, 3-OMe), 50.3 (s, C-13), 44.6 (d, C-14), 42.7 (q, 16-Me), 40.4 (d, C-9), 37.5 (d, C-8), 32.4 (t, C-12), 30.1 (t, C-15), 30 (t, C-6), 27.1 (t, C-7), 25.2 (t, C-11) and 13 (q, C-18) (Found: M^+, 314. $C_{20}H_{26}O_3$ requires M, 314).

This was followed by mixed fractions (1.23 g, 62%) (*ca* 1:1 from NMR), and then by the isomeric 3-methoxy-17-methyl-16,17-secoestra-1,3,5(10)-trien-16,17-dione (**123**) (11 mg, 0.5%), ν_{max} 1716 (CO) cm^{-1}; δ_H (200 MHz) 1.15 (3H, s, 13β-Me), 2.19 (3H, s, 17-Me), 2.82 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.3 Hz, 4-H), 6.73 (1H,

dd, *J* 8.6 and 2.3 Hz, 2-H), 7.2 (1H, d, *J* 8.6 Hz, 1-H) and 9.81 (1H, br d, *J* 1.7 Hz, 16-H) (Found: M^+, 314. $C_{20}H_{26}O_3$ requires M, 314).

The mixed fractions (1.23g, 3.88 mmol) were dissolved in tetrahydrofuran (50 cm^3) and treated with M-methanolic potassium hydroxide (11.63 cm^3, 11.63 mmol) at 20°C. After 30 min, water and 3M-hydrochloric acid were added, and the solvents were removed under reduced pressure. The products were isolated by a similar work-up to that described above (chloroform) as a yellow crystalline residue (1.1 g). Chromatography on silica gel (110 g) using ethyl acetate-toluene (3:97) gave the 17a-homo enone (**111**) (288 mg, 15% overall from **118**).

This was followed by mixed fractions (190 mg), and then by 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-16-one (**124**) (290 mg, 15% overall from **118**), m.p. 143-146°C (from chloroform-hexane); $[\alpha]_D$ +119° (*c* 1.0) (lit.[106] m.p. 147°C; $[\alpha]_D$ +118°); ν_{max} 1663 (CO) cm^{-1}; δ_H (400 MHz) 1.07 (s, 3H, 13β-Me), 1.29 (1H, m, 7-H), 1.47 (1H, dq, *J* 3 x 11.7 and 2.6 Hz, 8α-H), 2.01 (1H, m, 7-H), 2.2 (1H, dd, *J* 17.4 and 14.2 Hz, 15α-H), 2.65 (1H, dd, *J* 17.4 and 3.8 Hz, 15β-H), 2.86 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.88 (1H, dd, *J* 9.9 and 0.8 Hz, 17-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.8 Hz, 2-H), 6.8 (1H, d, *J* 9.9 Hz, 17a-H) and 7.22 (1H, d, *J* 8.8 Hz, 1-H); δ_C (100 MHz) 200.2 (s, C-16), 161.9 (d, C-17a), 157.7 (s, C-3), 137.6 (s, C-5), 132.0 (s, C-10), 126.8 (d, C-17), 126.1 (d, C-1), 113.5 (d, C-4), 111.8 (d, C-2), 55.2 (q, 3-OMe), 46.8 (d, C-14), 43.1 (d, C-9), 38.7 (d, C-8), 37.6 (t, C-15), 37.3 (t, C-12), 36.2 (s, C-13), 29.8 (t, C-6), 26 (t, C-11), 25.7 (t, C-7) and 17.4 (q, C-18) (Found: C, 80.6; H, 8.2%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; M, 296).

3-*Methoxy*-17a-*homoestra*-1,3,5(10),15,17-*pentaen*-17a-yl 17a-*triisopropylsilyl ether*(**125**)

Triethylamine (0.76 cm^3, 5.1 mmol) and triisopropylsilyl trifluoromethanesulfonate (0.72 cm^3, 2.7 mmol) were added in succession to a stirred solution of the 17a-homo enone (**111**) (200 mg, 0.68 mmol) in dichloromethane (10 cm^3) at 20°C under nitrogen. After 1 h, saturated sodium hydrogen carbonate was added, and the mixture was extracted with dichloromethane. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated to dryness under reduced pressure, to yield a mobile oil. Flash chromatography on silica gel (30 g) using ethyl acetate-hexane (1:19) as eluent gave the *silyl dienyl ether* (**125**) (297 mg, 97%), m.p. 108-110°C (from acetone-methanol); $[\alpha]_D$ -58° (*c* 0.9); δ_H (200 MHz) 0.91 (3H, s, 13β-Me), 1.11 (3H, s, 17a-OSi[C*H*{CH_3}$_2$]$_3$), 1.14 (18H, d, *J* 1.6 Hz, 17a-OSi[CH{C*H*$_3$}$_2$]$_3$), 2.81 (2H, m, 6-H_2),

3.78 (3H, s, 3-OMe), 5.03 (1H, d, *J* 5.7 Hz, 17-H), 5.55 (1H, dd, *J* 9.3 and 2.6 Hz, 15-H), 5.9 (1H, ddd, *J* 9.3, 5.7 and 3.3 Hz, 16-H), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.23 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 164.5 (s, C-17a), 157.5 (s, C-3), 138.1 (s, C-5), 133 (s, C-10), 126.1 (d, C-1), 124.4 (d, C-16), 119.4 (d, C-15), 113.6 (d, C-4), 111.5 (d, C-2), 98.7 (d, C-17), 55.2 (q, 3-OMe), 49.2 (d, C-14), 43.6 (d, C-9), 39.2 (s, C-13), 36.8 (d, C-8), 33.2 (t, C-12), 30.1 (t, C-6), 26.5 (t, C-11), 25.9 (t, C-7), 18.2 and 18.1 (each q, 17a-OSi[CH{*C*H_3}$_2$]$_3$), 13.5 (q, C-18) and 12.9 (d, 17a-OSi[*C*H{CH_3}$_2$]$_3$) (Found: C, 76.7; H, 9.8%; M^+, 452. $C_{29}H_{44}O_2Si$ requires C, 76.9; H, 9.8%; M, 452).

3-*Methoxy*-17a-*homoestra*-1,3,5(10),15,17-*pentaen*-17a-*yl* 17a-*trimethylsilyl ether* (**126**)

a) Triethylamine (1.9 cm^3, 13.5 mmol) and trimethylsilyl trifluoromethanesulfonate (1.8 cm^3, 6.8 mmol) were added in succession to a stirred solution of the 17a-homo enone (**111**) (500 mg, 1.7 mmol) in dichloromethane (25 cm^3) at 20°C under nitrogen. After 1h, saturated sodium hydrogen carbonate was added, and the mixture was extracted with dichloromethane. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated under reduced pressure, to yield a pale yellow crystalline residue (789 mg). Flash chromatography on silica gel (50 g) using toluene as eluent gave the *silyl dienyl ether* (**126**) (600 mg, 96%), m.p. 81-83°C (from acetone-methanol); $[\alpha]_D$ -37° (*c* 1.2); δ_H (200 MHz) 0.26 (9H, s, 17a-OTMS), 0.87 (3H, s, 13β-Me), 2.88 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.06 (1H, d, *J* 5.6 Hz, 17-H), 5.59 (1H, dd, *J* 9.5 and 2.6 Hz, 15-H), 5.92 (1H, ddd, *J* 9.5, 5.6 and 3.2 Hz, 16-H), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.23 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 164.2 (s, C-17a), 157.5 (s, C-3), 138.1 (s, C-5), 132.9 (s, C-10), 126.1 (d, C-1), 124.4 (d, C-16), 120.2 (d, C-15), 113.6 (d, C-4), 111.5 (d, C-2), 100 (d, C-17), 55.2 (q, 3-OMe), 49.1 (d, C-14), 43.7 (d, C-9), 38.5 (s, C-13), 36.8 (d, C-8), 33 (t, C-12), 30 (t, C-6), 26.5 (t, C-11), 25.8 (t, C-7), 13.2 (q, C-18) and 0.2 (q, 17a-OTMS) (Found: C, 74.8; H, 8.8%; M^+, 368. $C_{23}H_{32}O_2Si$ requires C, 74.95; H, 8.8%; M, 368).

b) A solution of the enone (**111**) (50 mg, 0.17 mmol) in tetrahydrofuran (3 cm^3) was added to a solution of lithium diisopropylamide (0.88 mmol; 0.35 cm^3 2.5M n-butyllithium added to 0.25 cm^3 diisopropylamine in 0.4 cm^3 tetrahydrofuran at 0°C) at -78°C. After 45 min, chlorotrimethylsilane (0.25 cm^3, 2 mmol) was added and the mixture was warmed to 0°C. After a further 45 min, saturated ammonium chloride was added, and the mixture was extracted with chloroform. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and the solvent was removed

under reduced pressure to yield an oily residue (89 mg), which was chromatographed on silica gel (5 g) using toluene as eluent. This gave the silyl dienyl ether (**126**) (56 mg, 90%).

3-*Methoxy*-17a-*homoestra*-1,3,5(10),14,16-*pentaen*-17a-*one* (**127**)

a) Palladium(II) acetate (303 mg, 1.35 mmol) and potassium carbonate (467 mg, 3.38 mmol) were added to a stirred soluton of the triisopropylsilyl dienyl ether (**125**) (260 mg, 0.58 mmol) in acetonitrile (6 cm^3) and dichloromethane (6 cm^3). After 1 h of reflux, the mixture was cooled, filtered, and washed with chloroform. The solvents were removed under reduced pressure to yield a brown oil (390 mg), which was chromatographed on silica gel (40 g) using ethyl acetate-toluene (1:19) as eluent. First to elute was *dienone* (**127**) (11 mg, 6%), m.p. 111-113°C (from ethanol); $[\alpha]_D$ +471° (*c* 1.0); ν_{max} 1656 (CO) cm^{-1}; δ_H (400 MHz) 1.31 (3H, s, 13β-Me), 1.56 (1H, ddd, *J* 2 x 13.3 and 3.7 Hz, 12α-H), 2.13 (1H, m, 7-H), 2.23 (1H, ddd, *J* 13.3, 3.5 and 2.5 Hz, 12β-H), 2.94 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.06 (2H, m, *W* 17.3 Hz, 15- and 17-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), 7.14 (1H, dd, *J* 9.6 and 6.3 Hz, 16-H) and 7.21 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 207.1 (s, C-17a), 162.4 (s, C-14), 157.8 (s, C-3), 142.3 (d, C-16), 137.3 (C-5), 131.3 (s, C-10), 127.3 (d, C-1), 123.3 (d, C-15), 113.7 (d, C-4), 112.5 (d, C-17), 112.2 (d, C-2), 55.2 (q, 3-OMe), 50.6 (s, C-13), 46.5 (d, C-9), 41.6 (d, C-8), 36.4 (t, C-12), 30.1 (t, C-6), 27.2 (t, C-11), 25.3 (t, C-7) and 23.6 (q, C-18) (Found: C, 81.8; H, 7.6%; M^+, 294. $C_{20}H_{22}O_2$ requires C, 81.6; H, 7.5%; M, 294).

This was followed by mixed fractions (136 mg), and then by 15β-*acetoxy*-3-*methoxy*-17a-*homoestra*-1,3,5(10),16-*tetraen*-17a-*one* (**128**) (4 mg; 2%), m.p. 102-105°C (from diisopropylether); $[\alpha]_D$ -141° (*c* 0.8); ν_{max} 1677 (CO) and 1733 (OAc) cm^{-1}; δ_H (400 MHz) 1.25 (3H, s, 13β-Me), 1.38 (1H, m, 7-H), 1.79 (1H, dq, *J* 3 x 11 and 2.6 Hz, 14α-H), 1.87 (1H, m, 7-H), 1.94 (1H, dd, *J* 10.9 and 4.2 Hz, 8β-H), 2.07 (3H, s, 15β-OAc), 2.12 (1H, dt, *J* 13.6 and 2 x 3.1 Hz, 12-H), 2.33 (1H, m, 9α-H), 2.4 (1H, m, 11-H), 2.84 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.56 (1H, dd, *J* 5.2 and 2.6 Hz, 15α-H), 6.06 (1H, d, *J* 10.1 Hz, 17-H), 6.63 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 6.87 (1H, dd, *J* 10.1 and 5.2 Hz, 16-H) and 7.23 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 204.7 (s, C-17a), 170.3 (s, 15-OAc), 157.7 (s, C-3), 140.6 (d, C-16), 137.4 (C-5), 132.1 (s, C-10), 129.1 (d, C-17), 126.3 (d, C-1), 113.5 (d, C-4), 111.8 (d, C-2), 64.7 (d, C-15), 55.2 (q, 3-OMe), 46.5 (d, C-8), 44.3 (s, C-13), 42.8 (d, C-9), 35.7 (d, C-14), 33 (t, C-12), 29.9 (t, C-6), 25.7 (t, C-7), 25.5 (t, C-11), 20.8 (q, 15-OAc) and 19.9 (q, C-18) (Found: M^+, 354.184. $C_{20}H_{22}O_2$ requires M, 354.183).

b) In a separate experiment, the silyl dienyl ether (**125**) (466 mg, 1.03 mmol) was treated with palladium(II) acetate (280 mg, 1.2 mmol) and potassium carbonate (712 mg, 5.15 mmol) in acetonitrile (10 cm^3) and dichloromethane (10 cm^3) in a similar manner to that described above. The entire crude product after filtration and evaporation of the solvents (506 mg) was dissolved in deoxygenated toluene (15 cm^3), and palladium(II) acetate (3.5 mg, 0.015 mmol) and triphenylphosphine (40 mg, 0.15 mmol) were added successively. The mixture was refluxed under nitrogen for 2 h, then cooled, quenched with water, and extracted with ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated under reduced pressure to yield an oily residue (461 mg), which was chromatographed on silica gel (46 g) using ethyl acetate-toluene (1:24) as eluent, to give the dienone (**127**) (242 mg, 80%).

c) The trimethylsilyl dienyl ether (**126**) (86 mg, 0.29 mmol) was dissolved in acetonitrile (3 cm^3) and dichloromethane (3 cm^3), and palladium(II) acetate (135 mg, 0.6 mmol) and potassium carbonate (207 mg, 1.5 mmol) were added to the solution. The mixture was refluxed under nitrogen for 3 h, then cooled, and filtered through a Celite pad. The solids were washed with chloroform, and the solvents were then removed under reduced pressure, to yield a dark oil (177 mg). This was chromatographed on silica gel (18 g) using ethyl actetate-hexane (1:5) as eluent, to yield mixed fractions of dienone (**127**) and acetoxy enone (**128**) (50 mg) in similar proportons (1:2 from NMR) to those found above.

d) Iodosobenzene (58 mg, 0.27 mmol) was added portionwise to a stirred solution of the triisopropylsilyl dienyl ether (**125**) (100 mg, 0.22 mmol) in dichloromethane (3 cm^3), maintaining the temperature between -16 and -19°C. Thereafter, azidotrimethylsilane (0.07 cm^3, 0.53 mmol) was added over 15 min. The mixture was warmed to 20°C and allowed to stir for 1 h. The contents of the reaction vessel were then evaporated to dryness under reduced pressure to yield a yellow oil (160 mg). This was immediately dissolved in tetrahydrofuran (3 cm^3), and this solution was added to a mixture of 1.1 M-tetrabutylammonium fluoride (0.4 cm^3) in tetrahydrofuran (2 cm^3) containing pre-dried, crushed molecular sieves at 0°C. After 30 min, saturated ammonium chloride was added, and the products were extracted into chloroform. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a dark oil (89 mg) which was chromatographed on silica gel (10 g) using ethyl acetate-toluene (1:24) as eluent. Mixed fractions of unidentified material (71 mg) eluted first, followed by dienone (**127**) (10 mg, 15%).

e) In a similar experiment ot that described in (d), the silyl dienyl ether (**125**) (100 mg, 0.22 mmol) was treated with iodosobenzene and azidotrimethylsilane. Caesium fluoride (67 mg, 0.44 mmol) was added to a solution of the crude product (161 mg) in dimethylformamide (4 cm^3), and the mixture was stirred under nitrogen at 20°C for 5 h. Water was added, and the products were extracted into ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated to dryness to yield an oil (86 mg), which was chromatographed in a similar way to that described in (d) to yield the dienone (**127**) (11 mg, 17%).

Hydrolysis of the 15β-*Acetoxy* Δ^{16}-17a-*Ketone* (**128**)

a) Potassium carbonate (1g, 7.2 mmol) was added to a stirred solution of the mixture (1:2) of the dienone (**127**) and acetoxy enone (**128**) (400 mg, 1.35 mmol) in methanol (10 cm^3) at 20°C. After 24 h, water was added, and the products were extracted into chloroform. The combined organic phase was washed with saturated sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated to dryness, to yield a colourless oil (545 mg) which was adsorbed on to silica gel (45 g). Elution using ethyl acetate-toluene (1:19 → 1:4) gave the dienone (**127**) (170 mg, 46%), followed by 15β-*hydroxy*-3,16β-*dimethoxy*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* (**129**) (17 mg, 4%), m.p. 147-149°C (from acetone-hexane); $[\alpha]_D$ +39° (*c* 1.0); ν_{max} 3568 (OH) and 1700 (CO) cm^{-1}; δ_H (200 MHz) 1.36 (3H, s, 13β-Me), 2.26 (1H, s, 15β-OH, exch. by D_2O), 2.57 (1H, ddd, *J* 12.8, 5 and 1 Hz, 17α-H), 2.92 (2H, m, 6-H_2), 3.06 (1H, dd, *J* 12.8 and 12.4 Hz, 17β-H), 3.36 obsc. (1H, ddd, *J* 12.4, 5 and 3.2 Hz, 16α-H), 3.43 (3H, s, 16β-OMe), 3.78 (3H, s, 3-OMe), 4.42 (1H, m, *W* 8 Hz, 15α-H), 6.64 (1H, d, *J* 2.6 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.23 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 344. $C_{21}H_{28}O_4$ requires M, 344).

Third to elute was 15β-*hydroxy*-3-*methoxy*-17a-*homoestra*-1,3,5(10),16-*tetraen*-17a-*one* (**130**) (55 mg, 13%), m.p. 178-179°C (from acetone-hexane); $[\alpha]_D$ -70° (*c* 1.1); ν_{max} 3608 (OH) and 1675 (CO) cm^{-1}; δ_H (200 MHz) 1.28 (3H, s, 13β-Me), 2.93 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 4.56 (1H, dd, *J* 10.1 and 5.5 Hz, 15α-H), 6.02 (1H, d, *J* 10.1 Hz, 17-H), 6.66 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), 6.89 (1H, dd, *J* 10.1 and 5.5 Hz, 16-H) and 7.24 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 76.7; H, 7.75%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.74%; M, 312).

Last to elute was 15β-*hydroxy*-3,16α-*dimethoxy*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* (**131**) (32 mg, 7%), m.p. 175-178°C (from acetone-hexane); $[\alpha]_D$ +19° (*c* 1.1); ν_{max} 3612 (OH) and 1704 (CO) cm^{-1}; δ_H (200 MHz) 1.34 (3H, s, 13β-Me), 1.6 (1H, s, 15β-OH, exch. by D_2O), 2.51 (1H, ddd, *J* 14.4, 3.3 and 0.9 Hz, 17α-H), 2.92 (2H, m,

6-H_2), 3.18 (1H, dd, *J* 14.4 and 3.5 Hz, 17β-H), 3.38 (3H, s, 16α-OMe), 3.79 (3H, s, 3-OMe), 3.81 obsc. (1H, ddd, *J* 3.5, 3.4 and 3.3 Hz, 16β-H), 4.42 (1H, m, *W* 14 Hz, 15α-H), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.24 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 73.0; H, 8.2%; M^+, 344. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%; M, 344).

b) 0.1 M-Potassium hydroxide in methanol (6.8 cm^3, 0.7 mmol) was added dropwise to a solution of the mixture (1:2) of dienone (**127**) and acetoxy enone (**128**) (100 mg, 0.34 mmol) in tetrahydrofuran (4 cm^3) at 0°C under nitrogen. After 1 h, water was added, and the mixture was acidified with M-hydrochloric acid. The mixture was extracted with chloroform, the combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The partially crystalline residue (196 mg) was chromatographed on silica gel (20 g) using ethyl acetate-toluene (1:19) as eluent, to yield the dienone (**127**) (49 mg, 50%), followed by 15β-*acetoxy*-3,16α-*dimethoxy*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* (**132**) (34 mg, 26%) as a non-crystalline product, ν_{max} 1737 (OAc) and 1708 (CO) cm^{-1}; δ_H (200 MHz) 1.31 (3H, s, 13β-Me), 1.96 (1H, dd, *J* 10.9 and 2.8 Hz, 14α-H), 2.12 (3H, s, 15β-OAc), 2.51 (1H, ddd, *J* 14.7, 2.8 and 1.2 Hz, 17α-H), 2.86 (2H, m, 6-H_2), 3.02 (1H, dd, *J* 14.7 and 3.7 Hz, 17β-H), 3.40 (3H, s, 16α-OMe), 3.78 (3H, s, 3-OMe), 3.81 obsc. (1H, ddd, *J* 3.5, 3.4 and 3.3 Hz, 16β-H), 4.42 (1H, m, *W* 14 Hz, 15α-H), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.24 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 344. $C_{21}H_{28}O_4$ requires M, 344).

3-*Methoxy*-16α-*methyl*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* (**133**)

Methyllithium (1.5M, 0.41 cm^3, 0.6 mmol) was added to a stirred suspension of copper(I) iodide (58 mg, 0.3 mmol) in diethyl ether (3 cm^3) at 0°C under nitrogen. To the resulting clear solution of lithium dimethylcuprate was added the enone (**111**) (75 mg, 0.25 mmol) in tetrahydrofuran (3 cm^3). The mixture was stirred under nitrogen at 0°C for 45 min, then quenched with saturated ammonium chloride, and extracted with chloroform. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated to dryness under reduced pressure to yield a colourless oil (77 mg), which was chromatographed on silica gel (8 g) using ethyl acetate-toluene (1:24) as eluent.This yielded the 16α-*methyl* 17a-*ketone* (**133**) (60 mg, 77%), m.p. 96°C (from chloroform-methanol); $[\alpha]_D$ -8° (*c* 0.5); ν_{max} 1693 (CO) cm^{-1}; δ_H (200 MHz) 1.0 (3H, d, *J* 7.1 Hz, 16α-Me), 1.11 (3H, s, 13β-Me), 2.06 (1H, dd, *J* 14.3 and 4.1 Hz, 17β-H), 2.8 obsc (1H, dd, *J* 14.3 and 6.2 Hz, 17α-H), 2.86 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d,

J 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 80.5; H, 9.0%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; M, 312).

3-*Methoxy*-17a-*oxo*-17a-*homoestra*-1,3,5(10)-*triene*-16α-*carbonitrile* (**134**)

The enone (**111**) (100 mg, 0.34 mmol) in benzene (6 cm^3) was treated with M-diethylaluminium cyanide (2 cm^3, 2 mmol) at 20°C under nitrogen. After 2 h, saturated ammonium chloride was added, and the mixture was poured into M-hydrochloric acid (20 cm^3). The product was extracted into ethyl acetate. The solvent was removed under reduced pressure, to give a crystalline residue (138 mg) which was chromatographed on silica gel (19 g) using ethyl acetate-toluene (1:9) as eluent, to afford 16α-*cyano* 17a-*ketone* (**134**) (68 mg, 64%), m.p. 219-222°C (from chloroform-methanol); $[\alpha]_D$ -4° (*c* 0.6); ν_{max} 2240 (CN) and 1709 (CO) cm^{-1}; δ_H (400 MHz) 1.11 (3H, s, 13β-Me), 2.32 (1H, br dt, 9α-H), 2.41 (1H, dq, *J* 13.6 and 3 x 3.3 Hz, 11α-H), 2.53 (1H, ddd, *J* 14.8, 2.3 and 1.8 Hz, 17α-H), 2.84-2.89 (2H, m, 6-H_2), 2.88 obsc (1H, dd, *J* 14.8 and 7 Hz, 17β-H), 3.41 (1H, m, *W* 18 Hz, 16β-H), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.4 Hz, 1-H); δ_C (50 MHz) 210.4 (s, C-17a), 157.6 (s, C-3), 137.3 (s, C-5), 131.8 (s, C-10), 126.2 (d, C-1), 120.7 (s, 16-CN), 113.4 (d, C-4), 111.7 (d, C-2), 55.1 (q, 3-OMe), 48.2 (C-13), 45.8 (s, C-14), 42.5 (d, C-8), 38.2 (d, C-9), 38.15 (t, C-17), 32 (t, C-12), 29.7 (t, C-6), 27.8 (d, C-16), 26.4 (t, C-11), 25.5 (each t, C-7 and C-15) and 16.6 (q, C-18) (Found: C, 77.7; H, 7.85; N, 4.4%; M^+, 323. $C_{21}H_{25}NO_2$ requires C, 78.0; H, 7.8; N, 4.3%; M, 323).

This was followed by mixed fractions (21 mg).

Conjugate Allylation of the Δ^{16}-17a-*Ketone* (**111**)

a) Titanium tetrachloride (1.4M solution in dichloromethane, 0.15 cm^3, 0.21 mmol) in dichloromethane (1 cm^3) was added dropwise to a solution of the enone (**111**) (20 mg, 0.07 mmol) in dichloromethane (1 cm^3) at -78°C under nitrogen. The orange suspension was stirred for 15 min, then allyltrimethylsilane (0.75M solution in dichloromethane, 0.15 cm^3, 0.11 mmol) in dichloromethane (1 cm^3) was added over 10 min. The resulting red suspension was stirred at -78°C for 4 h, then water (0.8 cm^3) was added, and the mixture was allowed to warm to 20°C. The product was extracted into chloroform, to yield a colourless oil (15 mg). Flash chromatography of this residue on silica gel (4 g) using ethyl acetate-hexane (1:4) as eluent gave 16α-*allyl*-3-*methoxy*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* (**135**) (9.6 mg, 42%), m.p. 104-107°C (from acetone-methanol); $[\alpha]_D$ +3°

(*c* 0.5); ν_{max} 1693 (CO) cm^{-1}; δ_H (200 MHz) 1.12 (3H, s, 13β-Me), 2.75 (1H, dd, *J* 13.9 and 5.4 Hz, 17β-H), 2.84 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.0 (2H, m, 3'-H_2), 5.73 (1H, dddt, *J* 18.5, 11.2 and 2 x 7 Hz, 2'-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 81.3; H, 9.1%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; M, 338).

This was followed by starting material (7 mg, 35%).

b) A solution of the enone (**111**) (20 mg, 0.07 mmol) in dimethylformamide (0.8 cm^3) was added to a stirred suspension of tetrabutylammonium fluoride (1.1 M in tetrahydrofuran, 0.05 cm^3, 0.055 mmol) and crushed, activated molecular sieves (*ca* 1 g) in dimethylformamide (1 cm^3) at 20°C under nitrogen. A solution of hexamethylphosphoric triamide (0.12 cm^3, 0.7 mmol) and allyltrimethylsilane (0.11 cm^3, 0.7 mmol) in dimethylformamide (1 cm^3) was added dropwise to the mixture, and stirring was continued for 1 h. M-Hydrochloric acid in methanol (0.8 cm^3) was added, and the mixture was poured into water (20 cm^3), and extracted with ethyl acetate. The organic layer was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and the solvent was removed under reduced pressure, to give a yellow oil (23 mg), which was flash chromatographed on silica gel (4 g) using ethyl acetate-hexane (1:4) as eluent. This yielded the allyl ketone (**135**) (11 mg, 48%) followed by starting material (5 mg, 25%).

Conjugate Methylation of 3-*Methoxy*-17a-*homoestra*-1,3,5(10),14,16-*pentaen*-17a-*one* (**127**)

a) Methylmagnesium iodide (1.56 mmol) was prepared in the usual way from magnesium (40 mg) and methyl iodide (0.1 cm^3) in diethyl ether (3 cm^3) and cooled to 0°C. Hexamethylphosphoric triamide (0.54 cm^3, 3.12 mmol) and copper(I) iodide-dimethyl sulfide complex (6 mg, 10 mol%) were added successively to the mixture. The dienone (**127**) (76 mg, 0.26 mmol) and chlorotrimethylsilane (0.4 cm^3, 3.12 mmol) in tetrahydrofuran (3 cm^3) were added over 15 min. After 30 min at 0°C, saturated ammonium chloride was added, and the mixture was extracted with chloroform. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated under reduced pressure, to yield a mobile oil (740 mg). Flash chromatography of this residue on silica gel (70 g) using toluene as eluent gave colourless, crystalline material, formulated as a 1:1 mixture (from NMR) of the epimers of 3-methoxy-16ξ-methyl-17a-homoestra-1,3,5(10),14-tetraen-17a-one (**136** and **137**) (55 mg, 69%). Two recrystallisations from chloroform-methanol and ethanol concentrated one isomer with respect to the other. The major isomer present in the crystal form, formulated as the 16α-

methyl epimer (**136**), had m.p. 124-130°C; ν_{max} 1701 (CO) cm^{-1}; δ_H (400 MHz) 1.1 (3H, d, *J* 6.9 Hz, 16α-Me), 1.29 (3H, s, 13β-Me), 2.38 obsc (1H, dd, *J* 12.8 and 9.3 Hz, 17β-H), 2.5 (1H, dd, *J* 12.8 and 5.5 Hz, 17α-H), 2.91 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.44 (1H, br d, *J* 2.8 Hz, 15-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.2 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 310. $C_{21}H_{26}O_2$ requires M, 310).

The mother liquor was slightly enriched with respect to the 16β-methyl epimer (**137**), m.p. 115-122°; ν_{max} 1701 (CO) cm^{-1}; δ_H (400 MHz) 1.05 (3H, d, *J* 7.1 Hz, 16β-Me), 1.27 (3H, s, 13β-Me), 2.25 obsc (1H, dd, *J* 14.9 and 8.7 Hz, 17β-H), 2.67 (1H, dd, *J* 14.9 and 6.1 Hz, 17α-H), 2.92 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.48 (1H, br d, *J* 2.1 Hz, 15-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.2 (1H, d, *J* 8.7 Hz, 1-H) (Found: M^+, 310. $C_{21}H_{26}O_2$ requires M, 310).

b) Methyllithium (1.5M, 0.41 cm^3, 0.6 mmol) was added to a stirred suspension of copper(I) iodide (58 mg, 0.3 mmol) in diethyl ether (3 cm^3) at 0°C under nitrogen. To the resulting clear solution of lithium dimethylcuprate was added the dienone (**127**) (75 mg, 0.26 mmol) in tetrahydrofuran (3 cm^3). The mixture was stirred under nitrogen at 0°C for 1 h, then quenched with saturated ammonium chloride, and extracted with chloroform. The combined organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and evaporated to dryness under reduced pressure to yield a pale yellow oil (79 mg), which was chromatographed on silica gel (8 g) using ethyl acetate-toluene (1:34) as eluent. This gave a 1:1 mixture (from NMR) of the Δ^{14}-16-methyl 17a-ketones (**136** and **137**) (45 mg, 58%), followed by starting material (**127**) (20 mg, 27%).

Conjugate Hydrocyanation of 3-*Methoxy*-17a-*homoestra*-1,3,5(10),14,16-*pentaen*-17a-*one* (**127**)

M-Diethylaluminium cyanide (2 cm^3, 2 mmol) was added to a stirred solution of the dienone (**127**) (65 mg, 0.22 mmol) in benzene (5 cm^3) at 20°C under nitrogen. After 2 h, saturated ammonium chloride was added, and the mixture was poured into M-hydrochloric acid (20 cm^3). The products were extracted into ethyl acetate. The solvent was removed under vacuum, to give a dark oil (131 mg), which was subjected to chromatography on silica gel (20 g) using ethyl acetate-hexane (1:4) as eluent. First to elute was 3-*methoxy*-17a-*oxo*-17a-*homoestra*-1,3,5(10),14-*tetraene*-16α-*carbonitrile* (**138**) (20 mg, 31%), m.p. 169-172°C (from acetone-methanol); $[\alpha]_D$ +177° (*c* 0.7); ν_{max} 2243 (CN) and 1714 (CO) cm^{-1}; δ_H (200 MHz) 1.38 (3H, s, 13β-Me), 2.78 (1H, dd, *J* 13.7 and 6 Hz, 17β-H), 2.94 obsc (1H, dd, *J* 13.7 and 8.4 Hz, 17α-H), 2.92-3.0 (2H, m,

6-H_2), 3.68 (1H, m, *W* 20 Hz, 16β-H), 3.79 (3H, s, 3-OMe), 5.57 (1H, d, *J* 3.7 Hz, 15-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.2 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 209.8 (s, C-17a), 157.8 (s, C-3), 151.2 (s, 16-*C*N), 137.2 (s, C-5), 130.9 (s, C-10), 127.1 (d, C-1), 119.5 (s, C-14), 113.6 (d, C-4), 112.2 (d, C-2), 111.0 (d, C-15), 55.2 (q, 3-OMe), 48.1 (C-13), 44.4 (d, C-8), 40.7 (d, C-9), 37.8 (t, C-17), 34.7 (t, C-12), 30.1 (t, C-6), 27.7 (d, C-16), 27.2 (t, C-11), 25.7 (t, C-7), 22.3 (q, C-18) (Found: C, 78.2; H, 7.2; N, 4.4%; M^+, 321. $C_{21}H_{23}NO_2$ requires C, 78.5; H, 7.2; N, 4.4%; M, 321).

This was followed by mixed fractions (35 mg, 54%), and then by 3-*methoxy*-17a-*oxo*-17a-*homoestra*-1,3,5(10),14-*tetraene*-16β-*carbonitrile* (**139**) (10 mg, 16%), m.p. 174-177°C (from acetone-methanol); $[\alpha]_D$ +118° (*c* 0.5); ν_{max} 2223 (CN) and 1713 (CO) cm^{-1}; δ_H (400 MHz) 1.3 (3H, s, 13β-Me), 2.81 (1H, dd, *J* 13.8 and 7.7 Hz, 17β-H), 2.87 (1H, dd, *J* 13.8 and 6.1 Hz, 17α-H), 2.9-2.95 (2H, m, 6-H_2), 3.71 (1H, m, *W* 20 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 5.57 (1H, dd, *J* 3.6 and 1.5 Hz Hz, 15-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.75 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 209.8 (s, C-17a), 157.8 (s, C-3), 151.4 (s, 16-*C*N), 137.2 (s, C-5), 131.0 (s, C-10), 127.1 (d, C-1), 119.5 (s, C-14), 113.6 (d, C-4), 112.2 (d, C-2), 111.0 (d, C-15), 55.2 (q, 3-OMe), 48.0 (C-13), 44.5 (d, C-8), 40.7 (d, C-9), 38.0 (t, C-17), 35.6 (t, C-12), 30.1 (t, C-6), 27.5 (d, C-16), 27.3 (t, C-11), 25.7 (t, C-7), 21.3 (q, C-18) (Found: M^+, 321.172. $C_{21}H_{23}NO_2$ requires M, 321.173).

Conjugate Allylation of 3-*Methoxy*-17a-*homoestra*-1,3,5(10),14,16-*pentaen*-17a-*one* (**127**)

a) Titanium tetrachloride (0.037 cm^3, 0.34 mmol) in dichloromethane (0.5 cm^3) was added dropwise to a solution of the dienone (**127**) (100 mg, 0.34 mmol) in dichloromethane (3 cm^3) at -78°C under nitrogen. The suspension was stirred for 15 min, then allyltrimethylsilane (0.06 cm^3, 0.38 mmol) in dichloromethane (1 cm^3) were added over 10 min. The resulting mixture was allowed to warm slowly to -65°C over 1 h, then saturated ammonium chloride was added. The mixture was extracted with chloroform, and the organic phase was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), to yield a colourless oil (154 mg). Chromatography of this residue on silica gel (30 g) using ethyl acetate-toluene (1:49) as eluent gave a compound formulated as 3-methoxy-17^{1}ξ-trimethylsilylmethyl-14,17ξ-ethano-17a-homo-14ξ-estra-1,3,5(10),15-tetraen-17a-one (**140**) (16 mg, 12%); $[\alpha]_D$ -13° (*c* 1.5); ν_{max} 1702 (CO) cm^{-1}; δ_H (400 MHz) 0.02 (9H, s, 1'-TMS), 0.56 (2H, m, 1'-H_2), 1.08 (3H, s, 13β-Me), 1.12 (1H, dd, *J* 12.5 and 6.4 Hz, 17^2-H), 1.85 (1H, dd, *J* 12.5 and 8.9 Hz, 17^2-H), 2.18 (1H, m, 17^1-H), 2.66 (1H, m,

9α-H), 2.88 (2H, m, 6-H_2), 2.98 (1H, d, *J* 6.6 Hz, 17-H), 3.78 (3H, s, 3-OMe), 6.06 (1H, dd, *J* 8 and 6.6 Hz, 16-H), 6.46 (1H, d, *J* 8 Hz, 15-H), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 217.0 (s, C-17a), 157.6 (s, C-3), 139.0 (d, C-15), 137.8 (s, C-5), 132.3 (s, C-10), 126.9 (d, C-1), 123.5 (d, C-16), 113.5 (d, C-4), 111.9 (d, C-2), 57.5 (d, C-17), 55.2 (q, 3-OMe), 47.8 (s, C-14), 44.9 (s, C-13), 40.5 (d, C-8), 38.7 (d, C-9), 36.5 (t, C-17^2), 34.4 (t, C-12), 30.5 (t, C-6), 30.4 (d, C-17^1), 26.4 (t, C-11), 24.7 (t, C-1'), 23.2 (t, C-7), 18.7 (q, C-18) and 0.6 (q, 1'-TMS) (Found: M^+, 408. $C_{26}H_{36}O_2Si$ requires M, 408).

This was followed by mixed fractions (85 mg), and then by a mixture (1:1 from NMR) of the epimers of 16ξ-allyl-3-methoxy-17a-homoestra-1,3,5(10),14-tetraen-17a-one (**141** and **142**) (10 mg, 9%); ν_{max} 1706 (CO) cm^{-1}; δ_H (200 MHz) 1.28 and 1.3 (each 3H, s, 13β-Me), 2.82 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.0-5.15 (2H, m, 3'-H_2), 5.48 and 5.51 (each 1H, d, *J* 2.4 Hz, 15-H), 5.77 (1H, m, *W* 50 Hz, 2'-H), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.4 and 2.6 Hz, 2-H) and 7.22 (1H, d, *J* 8.4 Hz, 1-H) (Found: M^+, 336. $C_{23}H_{28}O_2$ requires M, 336).

b) A solution of the dienone (**127**) (100 mg, 0.34 mmol) in dimethylformamide (3.2 cm^3) was added to a stirred suspension of tetrabutylammonium fluoride (1.1 M in tetrahydrofuran, 0.25 cm^3, 0.28 mmol) and crushed, activated molecular sieves (*ca* 1 g) in dimethylformamide (5 cm^3) at 20°C under nitrogen. A solution of hexamethylphosphoric triamide (0.3 cm^3, 1.75 mmol) and allyltrimethylsilane (0.28 cm^3, 1.76 mmol) in dimethylformamide (2.5 cm^3) was added dropwise to the mixture, and stirring was continued for 15 min. M-Hydrochloric acid in methanol (4 cm^3) was added, and the mixture was poured into water (100 cm^3) and extracted with ethyl acetate. The organic layer was washed (saturated $NaHCO_3$, brine) and dried ($MgSO_4$), and the solvent removed under reduced pressure, to give an orange oil (120 mg), which was chromatographed on silica gel (15 g) using ethyl acetate-hexane (1:19) as eluent. This yielded the allyl enones (**141** and **142**) (88 mg, 77%) as an inseparable mixture (1:1 from NMR).

Conjugate Acetonylation of 3-*Methoxy*-17a-*homoestra*-1,3,5(10),14,16-*pentaen*-17a-*one* (**127**)

18M-Hydrochloric acid (0.4 cm^3) was added to a stirred solution of the dienone (**127**) (100 mg, 0.34 mmol) in acetone (5 cm^3), and the mixture was refluxed under nitrogen for 5 h. Water was added to the cooled mixture, and the products were extracted into ethyl acetate. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried

($MgSO_4$), and evaporated to dryness under reduced pressure. Chromatography of the oily residue (167 mg) on silica gel (17 g) using ethyl acetate-toluene (1:19) as eluent gave starting material (**127**) (30 mg, 30%), followed by an inseparable mixture (1:1 from NMR) of the 16-epimers of 16ξ-acetonyl-3-methoxy-17a-homoestra-1,3,5(10),14-tetraen-17a-one (**143** and **144**) (68 mg, 57%). The mixture had ν_{max} 1707 (CO) cm^{-1}; δ_H (200 MHz) 1.29 and 1.30 (each 3H, s, 13β-Me), 2.14 and 2.16 (each 3H, s, 3'-Me), 2.9 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.49 and 5.50 (each 1H, br s, 15-H), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.4 Hz, 1-H) (Found: M^+, 352. $C_{23}H_{28}O_3$ requires M, 352).

3-*Methoxy*-17a-*homoestra*-1,3,5(10),15,17-*pentaen*-17a-*yl Acetate* (**145**)

Isopropenyl acetate (2.6 ml, 24 mmol), acetic anhydride (2.6 ml, 28 mmol) and toluene-*p*-sulfonic acid (55 mg, 0.3 mmol) were added to the enone (**110**) (163 mg, 0.55 mmol), and the mixture was heated to reflux under nitrogen for 5 h. The mixture was cooled, added to ice, neutralised with solid sodium hydrogen carbonate, and extracted with chloroform. The combined organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure to yield an oily residue (207 mg). Chromatography of this material on silica gel (21 g) using ethyl acetate-toluene (3:97) as eluent gave the *dienyl acetate* (**145**) (20 mg, 11%), m.p. 116-118°C (from acetone-methanol); $[\alpha]_D$ +66° (*c* 0.4); ν_{max} 1751 (OAc) cm^{-1}; δ_H (400 MHz) 0.96 (3H, s, 13β-Me), 1.63 (1H, td, *J* 2 x 13.1 and 3.3 Hz), 1.84 (1H, dt, *J* 12.9 and 2 x 3.5 Hz), 2.2 (3H, s, 17a-OAc), 2.36 (1H, dt, *J* 11.8 and 2 x 2.8 Hz), 2.89 (2H, dd, *J* 8.7 and 3.9 Hz, 6-H_2), 3.77 (3H, s, 3-OMe), 5.68 (1H, d, *J* 5.7 Hz, 17-H), 5.83 (1H, dd, *J* 9.5 and 5.7 Hz, 15-H), 5.98 (1H, ddd, *J* 9.5, 5.7 and 3.3 Hz, 16-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.19 (1H, d, *J* 8.7 Hz, 1-H) (Found: C, 78.0; H, 7.8%; M^+, 338. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; M, 338).

This was followed by starting material (115 mg).

3-*Methoxy*-17a-*homoestra*-1,3,5(10),14,16-*pentaen*-17aβ-*ol* (**146**)

Sodium borohydride (22 mg, 0.6 mmol) was added portionwise to a stirred suspension of cerium(III) chloride heptahydrate (110 mg, 0.3 mmol) and the dienone (**127**) (50 mg, 0.17 mmol) in dichloromethane (5 cm^3) and methanol (2.5 cm^3) at 0°C under nitrogen. After 1 h, saturated ammonium chloride was added, and the mixture was extracted with chloroform. The organic layer was washed (M-HCl, saturated $NaHCO_3$, brine), dried

($MgSO_4$), and the solvent was removed under reduced pressure to yield a non-crystalline residue (58 mg). Chromatography of the oil on silica gel (5 g) using ethyl acetate-toluene (1:19) gave starting material (**127**) (2 mg, 4%), followed by the 17β-*alcohol* (**146**) (35 mg, 70%) as semi-crystalline material, ν_{max} 3606 (OH) cm^{-1}; δ_H (200 MHz) 1.0 (3H, s, 13β-Me), 1.62 (1H, s, 17aβ-OH, exch. by D_2O), 2.9 (2H, m, 6-H_2), 3.8 (3H, s, 3-OMe), 4.37 (1H, br s, 17aα-H), 5.64 (1H, *J* 9.4, 1.5 and 1 Hz, 17-H), 5.76 (1H, dd, *J* 6 and 1.5 Hz, 15-H), 5.88 (1H, dddd, *J* 9.4, 6, 2.9 and 0.8 Hz, 16-H), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.76 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.28 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 296. $C_{20}H_{24}O_2$ requires M, 296).

Attempted Acetylation of the $\Delta^{14,16}$ 17β-*Alcohol* (**146**)

The dienone (**127**) (170 mg, 0.58 mmol) was treated with cerium(III) chloride heptahydrate (780 mg, 2.1 mmol) and sodium borohydride (156 mg, 4.2 mmol) in dichloromethane (20 cm^3) and methanol (10 cm^3) in a similar manner to that described above. The crude residue after work-up (187 mg) was dissolved in pyridine (5 cm^3) and treated with acetic anhydride (0.15 cm^3, 1.74 mmol). The mixture was stirred at 20°C for 20 h, then poured into ice-water, and extracted with chloroform. The organic phase was washed (saturated $NaHCO_3$, brine), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting oil (177 mg) was chromatographed on silica gel (18 g) using ethyl acetate-toluene (1:99) as eluent, to yield 3-*methoxy*-17a-*methyl*-17a-*homo*-18-*norestra*-1,3,5(10),13,15,17-*hexaene* (**147**) (36 mg, 22%), m.p. 121-124 °C (from acetone-hexane); $[\alpha]_D$ -80° (*c* 1.1); δ_H (200 MHz) 2.29 (3H, s, 17a-Me), 3.82 (3H, s, 3-OMe), 6.72 (1H, d, *J* 2.4 Hz, 4-H), 6.79 (1H, dd, *J* 8.5 and 2.4 Hz, 2-H), 7.03-7.25 (3H, m, 15-, 16- and 17-H) and 7.35 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 278. $C_{20}H_{22}O$ requires M, 278).

Other, unidentified mixtures of products eluted next.

Chapter 8

CRYSTAL STRUCTURE DETERMINATIONS

Crystal Data for the Propano-Bridged 17α-Alcohol (**23**).
$C_{22}H_{30}O_2.{}_{1/4}H_2O$, *M*, 330.984; monoclinic, space group P_1, *a*=10.266(1), *b*=14.409(2), *c*=14.925(2) Å, α=116.464(1)°, β=94.202(9)°, γ=108.419(9)°, *V*=1814(15) Å^3, *Z*=4, D_c=1.21 mg m^{-3}, μ=0.041 mm^{-1}, *F*(000)=722. A colourless crystal of dimensions 0.3 x 0.4 x 0.5 mm was used for data collection.

Data Collection and Processing.
Data collection was performed at 293K on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo-*K*α radiation (λ=0.7107 Å) and the ω-2θ scan mode; 6641 reflections measured ($2.0 \leq 2\theta \leq 50.0°$; $-12 \leq h \leq 12$, $-17 \leq k \leq 17$, $-17 \leq l \leq 17$); 4739 independant reflections with $I > 2\sigma I$ (*R*=0.049). Accurate cell parameters were obtained by least squares analysis of the setting angles of 24 reflections in the range $16 \leq \theta \leq 17°$. Data were collected with variable scan width, aperture width, and scan speed. Three reference reflections were monitored periodically for intensity and orientation control. The data were corrected for Lorentz-polarization effects.

Structure Analysis and Refinement.
The structure was solved by direct methods using SHELXS-86[159] and refined by using SHELX76[160]. Final refinement was by blocked-matrix least squares and included anisotropic refinement of all non-hydrogen atoms. The hydroxyl hydrogens were located in a difference electron density map and constrained to ride at 1.0(3) Å from their parent oxygens. Other hydrogens were placed in geometrically calculated positions and linked to common isotropic temperature factors. Analysis and refinement details are: number of parameters=923; max/min residual electron density 0.24/-0.24 e Å^{-3}; *R* 0.049 and *Rw* 0.047.

The refined atom coordinates are given in Table 8.1 and full lists of bond lengths, bond angles, torsion angles, calculated hydrogen atomic coordinates, and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Table 8.1: Fractional Atomic Coordinates (x 10^4) and Thermal Parameters ($Å^2$ x 10^3)

Atom	*x/a*	*y/b*	*z/c*	*U*equiv.*
C(1)	5813(0)	2582(0)	4671(0)	55(3)
C(2)	7149(6)	3479(4)	4955(4)	60(3)
C(3)	7735(5)	4273(4)	5985(4)	57(3)
C(4)	7064(6)	4170(4)	6725(4)	61(3)
C(5)	5793(5)	3307(4)	6448(4)	53(3)
C(6)	5026(8)	3177(5)	7223(5)	96(4)
C(7)	4217(7)	2048(4)	7006(4)	78(3)
C(8)	3811(5)	1104(4)	5886(3)	45(2)
C(9)	3714(5)	1571(3)	5149(3)	38(2)
C(10)	5141(5)	2499(4)	5405(4)	44(3)
C(11)	3204(5)	666(4)	4018(3)	48(3)
C(12)	1832(5)	-301(4)	3813(3)	47(3)
C(13)	1993(5)	-831(4)	4474(3)	44(2)
C(14)	2475(5)	71(4)	5635(4)	48(3)
C(15)	1140(5)	326(4)	5837(4)	58(3)
C(16)	-134(5)	-763(4)	5044(4)	63(3)
C(173)	2794(6)	-464(4)	6284(4)	67(3)
C(172)	1485(7)	-1474(5)	6109(4)	78(4)
C(171)	652(6)	-2279(4)	4965(4)	66(3)
C(17)	511(5)	-1604(4)	4447(4)	52(3)
C(18)	2964(5)	-1476(4)	4075(4)	57(3)
O(19)	-377(5)	-2354(4)	3412(3)	66(2)
O(20)	9007(4)	5194(3)	6350(3)	83(3)
C(21)	9603(6)	5401(6)	5606(6)	97(5)

* *U*equiv. is 1/3 of the trace of the orthogonalised U_{ij} tensor

Crystal Data for the Cyclopenta[14,15] 4',17-*Diketone* (**61**).

$C_{22}H_{26}O_3$, *M*, 338.43; orthorhombic, space group $P2_12_12_1$, *a*=6.6130(10), *b*=8.466(2), *c*=31.826(4) Å, α=β=γ=90°, *V*=1781.8(5) $Å^3$, *Z*=4, D_c=1.262 mg m^{-3}, μ=0.082 mm^{-1}, *F*(000)=728. A colourless crystal of dimensions 0.31 x 0.44 x 0.44 mm was used for data collection.

Data Collection and Processing.

Data collection was performed at 298K on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo-*K*α radiation (λ=0.7107 Å) and the ω-2θ scan mode; 3384 reflections measured ($1.28 \leq \theta \leq 24.99°$; $-7 \leq h \leq 7$, $0 \leq k \leq 10$, $0 \leq l \leq 37$); 3120 independant reflections (R_{int}=0.0485). Accurate cell dimensions were obtained by least squares analysis of the setting angles of 24 reflections in the range $16 \leq \theta \leq 17°$. Data were collected with variable scan width, aperture width, and scan speed. Three reference reflections were monitored periodically for intensity and orientation control. The data were corrected for Lorentz-polarization effects, but not for absorption.

Structure Analysis and Refinement.

The structure was solved by direct methods using SHELXS-86[159] and refinement was performed onF_o^2 using SHELXL93.[161] Final refinement was by full-matrix least squares. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions and refined with a single common isotropic temperature factor. Analysis and refinement details are: number of parameters=229; max/min residual electron density 0.266/-0.303 e.Å^{-3}; final R indices (with $I > 2\sigma I$), *R* 0.0794 and *Rw* 0.2269; R indices (all data), *R* 0.1392 and *Rw* 0.4233; absolute structure parameter -4(4).

The refined atom coordinates are given in table 8.2 and full lists of bond lengths, bond angles, torsion angles, calculated hydrogen atomic coordinates, and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Crystallographic numbering differs from conventional numbering, with:

C(141) representing C(3')

C(142) representing C(4')

C(143) representing C(5')

Table 8.2: Fractional Atomic Coordinates (x 10^4) and Thermal Parameters (Å^2 x 10^3)

Atom	*x/a*	*y/b*	*z/c*	*U*equiv.*
C(1)	9190(8)	8750(7)	2091(2)	56(2)
C(2)	9683(9)	8852(7)	2513(2)	54(1)
C(3)	8465(9)	9746(6)	2770(2)	50(1)
O(1)	8802(7)	9906(5)	3197(1)	67(1)
C(19)	10377(11)	8975(8)	3381(2)	71(2)
C(4)	6848(9)	10536(7)	2609(2)	53(1)
C(5)	6354(7)	10420(6)	2181(2)	47(1)
C(6)	4546(9)	11310(8)	2013(2)	63(2)
C(7)	4469(9)	11384(7)	1535(2)	54(1)
C(8)	4806(7)	9739(6)	1359(2)	42(1)
C(9)	6971(7)	9219(6)	1457(2)	44(1)
C(10)	7510(7)	9468(7)	1918(2)	45(1)
C(11)	7298(8)	7531(6)	1317(2)	51(1)
C(12)	6828(8)	7312(6)	854(2)	49(1)
C(13)	4656(8)	7788(6)	739(1)	45(1)
C(18)	3150(10)	6545(7)	880(2)	60(2)
C(14)	4216(7)	9503(6)	890(2)	40(1)
C(141)	4077(11)	12091(7)	535(2)	64(2)
C(142)	1953(9)	11644(7)	664(2)	57(2)
O(2)	491(9)	12468(7)	643(2)	93(2)
C(143)	1987(7)	9958(7)	821(2)	48(1)
C(15)	5291(8)	10586(6)	558(2)	47(1)
C(16)	5170(10)	9641(7)	148(2)	61(2)
C(17)	4779(8)	7963(7)	260(2)	50(1)
O(3)	4704(6)	6860(5)	20(1)	62(1)

* *U*equiv. is 1/3 of the trace of the orthogonalised U_{ij} tensor

Chapter 9

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